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The clinical and cost effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation.

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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

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EXECUTIVE SUMMARY

Objective

The aim of this systematic review and economic evaluation is to assess the clinical and cost-effectiveness of topotecan as second-line treatment for small cell lung cancer (SCLC).

Epidemiology and background

Lung cancer is one of the most common cancers with SCLC accounting for approximately 10-20% of all lung cancers. Without treatment, SCLC has an aggressive clinical course, with life expectancy of between 6 weeks and 3.5 months. However, SCLC is initially very sensitive to chemotherapy and this is reflected in prolonged median survival rates. Second-line chemotherapy is offered to patients at relapse, and depends on the response and duration of response to first-line therapy, but generally consists of a repeat of the first-line chemotherapy regimen. However, for some relapsed patients, this may not be considered appropriate due to the development of resistance, contraindications or adverse events. In these patients, alternative chemotherapy regimens can be used. This assessment considers topotecan used within its licensed indications as second-line treatment for patients with relapsed SCLC.

Methods

A sensitive search strategy was designed and applied to eleven electronic bibliographic databases from 1990 to February 2009. Bibliographies of related papers were screened, key cancer resources and symposia were searched and experts were contacted to identify additional published and unpublished references. Manufacturer submissions to NICE were also searched. Titles and abstracts were screened for eligibility by two independent reviewers. Inclusion criteria were defined *a priori* and applied to the full text of retrieved papers by two reviewers using a standard form. Data extraction and assessment of methodological quality was undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion or recourse to a third reviewer at each stage. Authors of all the trials were contacted to clarify if participants met the licensed indication of topotecan. The trials were reviewed in a narrative synthesis with full tabulation of the results of all included studies. Meta-analysis was not undertaken due to clinical heterogeneity in the patient groups and comparator treatments.

An independent economic model was developed to estimate the cost effectiveness of topotecan (oral or IV) compared with Best Supportive Care (BSC) for patients with relapsed SCLC, for whom re-treatment with the first line regimen was not considered appropriate, from the perspective of the NHS and Personal Social Services (PSS). The model used survival analysis methods to derive estimates of mean survival for patients treated with topotecan or receiving BSC alone, which were combined with

Quality of Life (QoL) weights to derive estimates of mean quality adjusted life expectancy for patients receiving BSC alone or topotecan and BSC. The model includes an estimate of time to disease progression for patients receiving topotecan, to take account of the reduction in QoL following disease progression.

Categories of costs included in the model include drug use, chemotherapy administration and on-treatment monitoring, management of adverse events, monitoring for disease progression and palliative care. Resource use in the model was estimated from included RCTs, other published sources and advice from clinical experts. Drug costs were unit costs taken for the British National Formulary. Other unit costs were taken from published sources (including NHS Reference Costs) and from Southampton University Hospitals Trust.

The base case model has a five year time horizon. Costs and health outcomes in the model are discounted at 3.5%. The estimated costs, life years and Quality Adjusted Life Years (QALYs) for relapsed SCLC patients receiving topotecan and BSC and BSC alone in the model are presented. Results are reported as incremental cost per life year gained and incremental cost per QALY gained.

Results

Quantity and quality of studies

Ten publications describing five randomised controlled trials (RCTs) were included in the review of clinical effectiveness. One RCT compared oral topotecan and best supportive care (BSC) versus BSC alone; one trial compared intravenous (IV) topotecan against CAV (cyclophosphamide, doxorubicin and vincristine); two studies evaluated oral topotecan versus IV topotecan and one RCT compared IV topotecan with IV amrubicin. Assessment of methodological reporting and quality varied between the included studies. In three trials the risk of selection bias was uncertain due to a lack of reporting of the methods of generating the randomisation sequence and allocation concealment, whilst there was a risk of detection bias in all of the studies. Overall, methodological quality was judged to be good in two trials and unknown in three trials. For two trials, uncertainty remains as to whether the included participants fully met the licensed indication for topotecan and, as such, caution is needed when interpreting the results as the population groups may be slightly different than those eligible for topotecan according to the marketing authorisation.

Systematic searches identified no fully published economic evaluations of oral or IV topotecan for the treatment of relapsed SCLC, in patients who were not considered appropriate for re-treatment with their first line regimen, and only limited information on QoL/ utilities in patients with relapsed SCLC. The manufacturer's submission in support of topotecan, which included an economic evaluation of oral topotecan and BSC compared with BSC alone, was reviewed.

Summary of clinical effectiveness

There were no statistically significant differences between groups when IV topotecan was compared with either CAV or oral topotecan for overall response rate, the primary outcome in four RCTS. Response rate was seen to be significantly better in participants receiving IV amrubicin compared to IV topotecan (38% vs 13% respectively, p=0.039), although it should be noted that the dose of topotecan used (1.0 mg/m^2) was lower than the UK recommended dose (1.5 mg/m^2). In the trial assessing oral topotecan against BSC, response was only measured in those in the topotecan group as measurement of this outcome in the comparator (BSC alone) was not appropriate. Where reported, there were no statistically significant differences in time to disease progression for IV topotecan compared with either CAV or oral topotecan.

In one RCT with overall survival as the primary outcome, there was a statistically significant benefit in favour of oral topotecan + BSC compared with BSC alone (hazard ratio 0.61, 95% CI 0.43, 0.87, p=0.01). None of the remaining four RCTs showed any statistically significant differences in overall survival between treatment arms.

Only two trials measured QoL as an outcome. QoL data showed a significantly smaller decline in health status for those receiving topotecan in addition to BSC, although these results should be viewed with caution owing to issues surrounding the data reported. One of the trials comparing oral versus IV topotecan reported no statistical differences between groups, although no data was presented.

Generally, rates of adverse events were observed to be comparable across treatments in the included studies. Some haematological toxicities occurred significantly more frequently in the topotecan group compared with CAV, whilst rates of haematological toxicities in the topotecan versus amrubicin trial varied between arms. Toxicities observed with oral and IV topotecan were similar. Rates of adverse events and toxicities were not tested for statistical significance in the studies.

Summary of costs

Drug acquisition costs for four cycles of treatment (the mean number of cycles in trials of oral and IV topotecan), assuming a patient BSA of 1.8m^2, were estimated at £2,550 for oral topotecan and £5,979 for IV topotecan. Non-drug treatment costs (for chemotherapy administration and monitoring while on treatment) accounted for an additional £1,097 for oral topotecan (30% of total treatment costs, of which £743 (68%) is for chemotherapy administration) and £4,289 for IV topotecan (42% of total treatment costs, of which £3,936 (92%) is for chemotherapy administration).

Further costs are associated with the management of adverse events, which amount to £1,584 for oral topotecan (30% of total treatment cost) and £1,149 for IV topotecan (10% of total treatment cost). In both cases the majority of adverse event costs are associated with haematological toxicity.

Summary of cost effectiveness

The manufacturer's economic model, based on individual patient data from one RCT, compared oral topotecan and BSC with BSC alone. The QALY gain with oral topotecan and BSC was estimated at 0.211 in the base case analysis. The cost difference was £5,671, giving an ICER of £26,833 per QALY gained. Sub-group analyses suggested that oral topotecan may be more cost effective in patients whose time to progression from prior therapy was less than or equal to 60 days, in women and in those patients without liver metastases. Treatment with oral topotecan and BSC also appeared to be more cost effective for patients with a performance status of 2, as opposed to those with performance status of zero or 1.

In the independeant model the gain in discounted life expectancy associated with the addition of oral topotecan to BSC was 0.33 years (approximately 16.9 weeks) and the discounted QALY gain was 0.1830 QALYs. The incremental cost was approximately £6,194, resulting in an ICER of £33,851 per QALY with the addition of oral topotecan to BSC.

The gain in discounted life expectancy associated with IV topotecan, compared with BSC, in the independent model was 0.30 years (approximately 15.9 weeks) – one week shorter than the base case analysis for oral topotecan. The discounted QALY gain is between 0.1628 and 0.1910 QALYs, depending on assumptions regarding time to progression, while the incremental cost is approximately £12,000, resulting in an ICER between £65,507 and £74,074 per QALY gained, for IV topotecan compared with BSC. Compared with oral topotecan, IV topotecan is strictly dominated or is associated with a very high ICER.

Sensitivity analyses

In a deterministic sensitivity analysis using the manufacturer's model, the results were sensitive to methods of estimating QoL, drug administration costs and adverse event costs. Using a parametric cost effectiveness acceptability curve, the MS reported a probability of oral topotecan and BSC being cost effective, compared with BSC alone, of 22% at a willingness to pay threshold of £20,000 per QALY and 60% at a willingness to pay threshold of £30,000 per QALY.

In a deterministic sensitivity analysis using the independent model, the cost effectiveness results for oral topotecan and BSC were generally robust to variation in parameters values. The results were

most sensitive to assumptions over the form of survival functions adopted and variation in values of parameters in the survival functions, variation in utility estimates applied in the model and the cost of outpatient attendance for the administration of oral chemotherapy. In a probabilistic sensitivity analysis the probability of oral topotecan and BSC being cost effective, compared with BSC alone, was estimated at 0% using a willingness to pay threshold of £20,000 and a 20% probability using a willingness to pay threshold of £30,000 per QALY. A probabilistic sensitivity analysis for IV topotecan showed zero or very low probability of being cost effective, compared with BSC alone, at willingness to pay thresholds up to £50,000.

Conclusions

In summary, the clinical evidence indicates that topotecan is better than BSC alone in terms of improved survival, is as effective as CAV, and less favourable than IV amrubicin in terms of response. Oral topotecan and IV topotecan were shown to be similar in efficacy. It remains uncertain whether topotecan is more or less toxic than comparator interventions.

The cost effectiveness analysis showed that, for patients with relapsed SCLC, topotecan offers additional benefit over BSC, but at increased cost. Costs for IV topotecan are substantially higher than for oral topotecan, while health benefits are largely equivalent. ICERs for IV topotecan, compared with BSC are high and suggest it is unlikely to be a cost effective option for this group of patients. Oral topotecan is associated with a lower ICER, compared with BSC, although this remains at the upper extreme of the range conventionally regarded as cost effective from an NHS decision making perspective. Sensitivity analyses suggest the exact value of the ICER is highly dependent on assumptions regarding QoL for patients with relapsed SCLC receiving oral topotecan.

Recommendations for further research

- It is unlikely that any further RCTs of topotecan compared to BSC will be ethically acceptable, nor is it likely for there to be a need to undertake a further comparison with CAV therapy, and there is little to be gained from undertaking further evidence of the effectiveness of IV versus oral topotecan. However, given the ongoing RCTs of topotecan versus amrubicin it would be desirable to update the current review when these report.
- Further research is required into the QoL of patients with relapsed SCLC, to identify the impact of disease progression on QoL. In the case of patients receiving active treatment, further research is required on the impact of response (complete or partial response) and the impact of treatment-related adverse events on QoL.
- Further research on the impact of active treatment on resource use for palliative care would improve cost effectiveness models for topotecan. Data collection on resource use in the RCT by

O’Brien and colleagues was not comprehensive. It is difficult to determine whether the lower proportion of patients receiving radiotherapy and palliative medication (in the topotecan and BSC arm) indicates a genuine reduction in palliative care interventions or a postponement until disease progression occurs.

LIST OF ABBREVIATIONS

AC	Adenocarcinoma
ACE	Adriamycin (doxorubicin)/ cyclophosphamide/ etoposide
AWMSG	All Wales Medicines Strategy Group
BSA	Body Surface Area
BSC	Best supportive care
CANISC	Cancer Network Information System Cymru
CAV	Cyclophosphamide, adriamycin (doxorubicin) and vincristine
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
ECOG	Eastern Co-operative study Group
EQ-5D	EuroQol-5 Dimensions health questionnaire
ETS	Environmental tobacco smoke
FACT-L	Functional Assessment of Cancer Therapy - Lung questionnaire
GCSF	Granulocyte colony stimulating factor
GP	General Practitioner
GSK	GlaxoSmithKline
HR	Hazard ratio
HRQoL	Health related quality of life
ITT	Intention-to-treat analysis
IV	Intravenous
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
LUCADA	Lung Cancer Data
MDT	Multidisciplinary team
MS	Manufacturer's submission
NHS CRD	NHS Centre for Reviews and Dissemination
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PCI	Prophylactic cranial irradiation
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PSA	Patient symptom assessment scale
PSS	Personal Social Services
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumours
RBC	Red Blood Cell
RCT	Randomised controlled trial
SCLC	Small cell lung cancer
SCC	Squamous cell carcinoma
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TAR	Technology Assessment Report
TFI	Treatment-free interval
TNM	Tumour node metastases
TOI	Trial outcome index
TTP	Time to disease progression
UKCCCR	UK Coordinating Committee on Cancer Research
ULN	Upper Limit of Normal
VAS	Visual analogue scale
WHO	World Health Organisation

1 BACKGROUND

1.1 Description of underlying health problem

Lung cancer can be categorised into four major cell-types: small cell lung cancer (SCLC), squamous cell carcinoma (SCC), adenocarcinoma (AC) and large cell carcinoma.[1] The latter three cell-types are most often described as 'non-small cell lung cancer' (NSCLC). SCLCs are usually centrally located with extensive mediastinal involvement, tend to grow rapidly and spread quickly to distant sites (metastases).[2] SCLC is typically classified using a two-stage system, limited-stage disease and extensive-stage disease according to the level of progression of the disease. Limited-stage disease is generally confined to one hemi-thorax and its regional lymph nodes, in the absence of malignant effusion, and can be encompassed in one radiotherapy port. Extensive-stage disease is disease beyond the confines of the thorax at diagnosis, with the presence of systemic metastases, and cannot be encompassed safely in one radiotherapy port.[3] The prognosis for patients with extensive-stage disease is much poorer than for those with limited-stage disease. Most SCLCs present with metastases - a recent review found that two thirds of patients have extensive disease on presentation.[4]

In most patients the disease is symptomatic on presentation. In some, there are non-specific symptoms such as fatigue, anorexia, and weight loss, whilst in others there are more direct signs and symptoms such as breathlessness, chest discomfort and haemoptysis (blood stained sputum).[2] SCLC is also associated with systemic symptoms related to paraneoplastic syndromes.[5] These are caused by the release of bioactive substances produced by the tumour or in response to the tumour[2] and include endocrine syndromes and neurologic syndromes.[5] The most common endocrine syndrome in SCLC is inappropriate secretion of antidiuretic hormone (leading to water retention), hyponatraemia (low sodium), and hypotension (low blood pressure). Digital clubbing and hypertrophic pulmonary osteoarthropathy are common skeletal manifestations.[2]

SCLC is initially very sensitive to chemotherapy, with 60% to 90% of patients with limited-stage disease responding to first-line therapy and 40% to 70% of patients achieving a complete response (CR) (no further evidence of disease).[6] For extensive-stage disease, approximately 50-85% respond to first-line therapy.[7]

Aetiology

Risk factors for lung cancer include tobacco exposure, occupational exposure, gender, diet and chronic lung disease. Smoking is the leading cause of lung cancer, accounting for approximately 80-90% of cases[8,9] although it is likely that the cause of lung cancer is multifactorial and involves more than a simple association with smoking.[10] When compared to people who have never smoked, those who have smoked without quitting successfully have a 20-fold increase in lung cancer risk.[11] The risk

for lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day.[11] The association with smoking has been shown to be much stronger in SCLC than NSCLCs in a meta-analysis.[12] Passive smoking (referred to as environmental tobacco smoke [ETS]) is also associated with lung cancer, albeit more weakly than active smoking.[8]

Lung cancer was initially seen at higher rates in males, being associated with an earlier start of smoking tobacco and the higher quantities of tobacco smoked.[8,10] However, the disease has been declining in recent years in males, but increasing in women, most likely due to changes in smoking practices.[10,12] Whether men and women differ in their susceptibility to the carcinogens in tobacco smoke remains the focus of controversy. Some studies report that women who smoke have a significantly larger relative increase in lung-cancer risk than men.[13] Other studies, however, have found that there do not appear to be differences between men and women in their susceptibility to lung cancer given comparable smoking histories.[12,14] A recent cohort study[13] of 279,214 men and 184,623 women, for example, suggests that women are not more susceptible than men to the carcinogenic effects of cigarette smoking.

Occupational exposure to compounds such as asbestos, radon, chromium, and nickel have also been recognised to be risk factors for lung cancer.[15] A diet rich in fruits and vegetables is associated with a reduced risk of lung cancer in smokers, ex-smokers and those who have never smoked.[8,16] Some studies have also shown an association between dietary beta-carotene intake and a lower risk of lung cancer.[8] However, intervention trials of beta-carotene supplementation have either shown no effect, or an increased risk of lung cancer.[16] Other dietary factors that may have an association with a higher risk of lung cancer are high fat and cholesterol content, meat consumption, high intakes of dairy products and high consumption of alcohol.[16] However, because tobacco smoking has such an overwhelming contribution to the risk of lung cancer, it is often difficult to assess whether dietary factors independently are risk factors for lung cancer.[8,16]

An increased susceptibility to lung cancer may also result from the presence of previous lung disease.[10] Associations have been noted in the literature, but, as with the association with dietary factors, these are also possibly confounded by tobacco smoking and therefore findings are contestable.[8] Chronic obstructive pulmonary disease (COPD) has been shown to be an independent predictor of lung cancer risk in some studies however.[10]

Diagnosis and Staging

Lung cancer is usually suspected on the basis of an initial clinical assessment – taking into account the patients' symptoms, history, and a physical examination – in addition to an abnormal chest x-ray. Confirmation of the diagnosis is then achieved using histological and cytological tests. Patients with

SCLC are generally staged by clinical evaluation and computerised tomography of the chest and abdomen.[3,17] The TNM (Tumour Node Metastases) stage scores are not usually relevant in SCLC due to the high proportion of patients presenting with metastases and its poor prediction of survival.[4,17] As previously mentioned, SCLC is classified as limited-stage disease or extensive-stage disease, classified according to the level of progression of disease. Selection of the most appropriate treatment is determined primarily by the stage of disease (see current service section below).

Performance status

Measurement of the functional status of a patient is often described in terms of the World Health Organisation/Eastern Co-operative study Group (WHO/ECOG) performance status scores.[18] This scale rates the effect on daily living on a scale of 0-5 where 0 is 'fully active, able to carry on all pre-disease performance without restriction', 4 is 'completely disabled, cannot carry out any self-care, totally confined to bed or chair' and 5 is 'dead' (see Appendix 1). The Karnofsky performance status scale, can also be used to measure functional status in SCLC. This is a 100-point scale, rating performance from death (zero), through inability to care for self, to able to carry on normal activity with no evidence of disease (100)[19] (for full details see Appendix 1).

Epidemiology

Lung cancer is one of the most common cancers in England, accounting for some 15% of all malignancies in males and 11% in females in 2005.[20] Lung cancer is the most common cause of death from cancer worldwide.[21-23] The proportion of lung cancer cases classified as small cell type has been steadily falling over the years. The reasons for this are unclear, but it has been attributed to changing smoking habits.[8,12,24] Cancer statistics do not appear to distinguish between the different histological types of lung cancer in their rates. However, estimates suggest that small cell lung cancers account for approximately 10-20% of lung cancers, with rates in more recent estimates reflecting the lower end of this range.[3,25,26] Therefore, crude estimates of the epidemiology of SCLC can be generated from the overall rates of lung cancer.

There were 33,181 new cases of lung cancer in England and Wales in 2005[20,27] with more cases in males than in females (19,261 males, 13,920 females). European age-standardised incidence rates of lung cancer in England in 2005 were 72.9 per 100,000 in males and 50.6 per 100,000 in females.[20] The corresponding rates in Wales in 2005 were 62.5 per 100,000 (males) and 39.5 per 100,000 (females).[27] In 2006, estimates of the age-standardised incidence rates of lung cancer in the UK were lower than estimates for all European Union countries for males (57.1 per 100,000 compared to 71.8 per 100,000) but higher for females (34.6 per 100,000 versus 21.7 per 100,000).[21] Taking a range of 10-20% for SCLC, an estimate of the number of new cases of SCLC per year (using 2005 estimates for England and Wales[20,27]) would be in the region of 3,300 – 6,600 for England and Wales.

The incidence of lung cancer rises with increasing age. Very few people are diagnosed under the age of 40 years, and the incidence shows a peak in rates around ages 75-84 years. Most cases occur in people over the age of 60 years.[28] Time trends in the incidence of lung cancer show an overall decline in rates between 1995 and 2004.[28] Recently, the National Lung Cancer Audit was set up in England and Wales to collect information on lung cancer with the aim of understanding incidence, treatments, and outcomes and to explore regional variations. The report for the period 2006-7[26] presents data derived from the LUCADA (Lung Cancer Data) database in England and via the Cancer Network Information System Cymru (CANISC) in Wales and includes data from 93% of trusts from these countries. This showed that the incidence of lung cancer is clearly associated with the degree of deprivation; there was more than a two-fold difference in incidence between the most affluent groups and the most deprived groups.[26] The report confirms the positive association between deprivation and levels of smoking, which may account for much of this difference.

Prognosis

Lung cancer is the most common cause of death from cancer in both men and women.[22,23] The survival rate has improved in recent years,[29] although deaths from lung cancer remain high (5-year age-standardised survival rate of 5.8% and 6.4% in males and females respectively in 1996-1999) in the UK.[29] This is partly owing to diagnosis often being at a late stage, when curative treatments are not possible.[30] SCLCs tend to grow rapidly and have a greater tendency to widely metastasise.[10] An important predictor of prognosis in SCLC is the extent of disease progression. Without treatment, SCLC has an aggressive clinical course, with life expectancy of about 3.5 months for limited-stage disease and six weeks for extensive-stage disease.[31] With treatment, median survival for patients with limited-stage disease is 16 to 22 months; for those with extensive-stage disease median survival is 10 months.[32] Approximately 20%–40% of patients with limited-stage SCLC and fewer than 5% of patients with extensive-stage SCLC survive 2 years.[33] Survivors often continue to relapse up to, and occasionally after, five years. However, for those surviving long-term, relapse after 5-6 years appears to be a rare event,[34] although in one study, longer-term survivors appeared to be at high risk of a second primary cancer.[34]

Prognostic factors have been reported by a number of studies in the literature and while comparisons are not necessarily easy to make between these different studies, a number of key variables do appear to be consistently identified as having an effect on prognosis. In a review for the Lung Cancer Subcommittee of the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) in 1990, Rawson and Peto[35] identified a number of variables which contributed significantly to the prediction of likely survival over the six months after starting treatment. They demonstrated that performance status, alkaline phosphatase and disease stage were the most important prognostic

factors. More recent epidemiological studies show similar results. Lassen and colleagues[36] studied prognostic factors that correlated with survival after 18-months in a retrospective review of 1,714 SCLC patients. The extent of disease and the performance status were found to be of prognostic significance. In limited-stage disease, an elevated lactate dehydrogenase (LDH) (an enzyme that is often raised in cancers and can be used as a marker of disease) was considered unfavourable. In this study gender appeared to have no significant influence on survival.[36] Similar findings were observed in an analysis by the South West Oncology Group in the USA, although in this study female gender was seen to be an additional independent favourable predictor.[37] In this latter study, predictors of survival in those with extensive-stage SCLC were the number of metastatic sites, with lower numbers of sites being related to better prognosis. In an exploratory analysis of patients from four European clinical trials, characteristics that were associated with a higher objective response rate included higher performance status, limited-stage disease, and absence of brain metastases.[38] This study also found that women fared better than men,[38] as did an analysis of prognostic factors from a five-year RCT.[39] Prominent prognostic factors among all SCLC patients in this latter study were also extent of disease, LDH levels and weight loss.[39] SCLC is frequently associated with paraneoplastic syndromes (above) which can be caused by either ectopic hormone production or antibody-mediated tissue destruction.[33] Ectopic hormone production is the synthesis and secretion of a hormone by a tumour of a tissue that does not normally produce the particular hormone, and it has been associated with extensive-stage SCLC and a poorer outcome.[40] Antibody-mediated paraneoplastic syndromes are however associated with more favourable outcomes.[33,40]

1.2 Current service provision

Selection of the most appropriate first-line treatment for SCLC is determined primarily by the stage of disease. Treatments include chemotherapy, radiotherapy or a combination of these treatments, with increased survival attributed to combination therapy.[41] The majority of SCLC patients are inoperable,[42] as the disease is often widespread at the time of diagnosis.[5]

The current NICE guidelines[3] recommend that patients with SCLC should be offered a multi-drug platinum-based chemotherapy as first-line therapy. Those with limited-stage disease should be offered radiation concurrently with the first or second cycle, or following completion if a good partial response is seen within the thorax. Their initial treatment is usually followed by prophylactic cranial irradiation, in order to reduce the risk of cerebral metastases.[26] For those with extensive-stage disease, prophylactic cranial radiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response in the thorax.[43]

The platinum-based treatment combinations for first-line therapy that are offered (and recommended by NICE) are either cisplatin or carboplatin with etoposide. Other active agents include anthracyclines (doxorubicin, epirubicin), alkylating agents (cyclophosphomide, ifosfamide), vinca alkaloids (vindesine, vincristine) and taxanes (paclitaxel).

While guidelines for rapid referral of patients exist, there are many routes of patient referral.[26] Only 48% of patients are directly referred to specialist lung cancer teams via their GP, possibly due to the non-specific nature of lung cancer symptoms.[26] The majority of trusts in England and Wales now have rapid access clinics, managed by a multidisciplinary team (MDT).[26] The national lung cancer audit report 2006-2007 asserts that outcomes for lung cancer patients in the UK vary widely across the country and are poor when compared to many other countries.[26] The specialist nature of cancer treatments means that patients are often treated by more than one trust.[26] Despite NICE's recommendation that all patients are reviewed, figures suggest that this only occurs in 86% of cases.[26] Specific anti-cancer treatment such as chemotherapy and radiotherapy as first line treatment are suggested to remain low by international standards.[26] In addition, the likelihood of receiving chemotherapy in the UK declines rapidly for anyone over 75 years of age.[26] The report suggests that whilst prognosis for lung cancer patients has remained poor with little improvement in long term survival, applying best practice could provide a considerate improvement in outcomes.[26]

Objective tumour response is assessed by x-ray or CT scan. A response requires the tumour to reduce by at least 30% using a unidimensional measure such as the Response Evaluation Criteria In Solid Tumours (RECIST) or 50% using a bidimensional measure (WHO), and maintained for at least four weeks (see Appendix 1). Response to first-line therapy for SCLC can be categorised as either sensitive, resistant, or refractory.[6] Sensitive refers to a tumour response of more than 90 days, resistant to tumour recurrence within 90 days and refractory to tumours that either never responded or progressed during first-line therapy. It is generally thought that those with a sensitive response will have the greatest potential for second-line therapy.[6]

Second-line treatment decisions depend on the response to first line therapy and the duration of that response.[3,44] Evidence suggests that the best results from second-line chemotherapy are achieved in those with at least three months between response and progression.[4] On relapse, re-treatment with the same chemotherapy regimen is reasonable if a durable first-line response is achieved. For other patients, this may not be appropriate due to a short duration of response, the development of resistance or other contraindications.[45] In these patients, alternative chemotherapy regimens can be used.[46]

IV topotecan has been assessed by the Scottish Medicines Consortium (SMC) (which makes recommendations to the NHS in Scotland), but was not recommended for the treatment of patients with relapsed SCLC, "for whom re-treatment with the first-line regimen is not considered appropriate".[47] In contrast, the All Wales Medicines Strategy Group (AWMSG) has recommended IV topotecan for "use within NHS Wales for the treatment of patients with relapsed small SCLC for whom re-treatment with the first-line regimen is not considered appropriate".[48] However, the AWMSG also noted that topotecan should only be initiated by specialists experienced in the treatment of SCLC and it was not recommended for shared care.

UK research using a 4-year retrospective patient chart analysis, determined the average cost for the treatment of SCLC patients using a variety of sources.[49] The calculated cost per patient from a cohort of 109 patients was £11,556, with the most expensive element through all phases of the disease being hospitalisation.[49] The average patient cost for first-line treatment was estimated at £6,128 (48.7% of total costs), with 28% of the total costs down to recurrence of the disease until death. The average cost per patient for second-line treatment was around £5,008.[49]

1.3 Description of new intervention

Topotecan is an anti-cancer treatment which acts by the inhibiting the enzyme topoisomerase I, which is required for DNA replication. This leads to cell death.

Topotecan is indicated for patients as a second-line therapy in those with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate. The marketing authorisation for intravenous (IV) therapy was granted in the UK in 2006 and more recently a license was granted for oral therapy (2008). The recommended dose for IV treatment is 1.5mg/m^2 of body surface area a day in a 30-minute infusion for five consecutive days, in a 21-day cycle. The cost of IV topotecan is £97.65 per mg, which equates to £147.47 m^2/day.[50] For oral treatment the recommended dose is 2.3 mg/m^2/day, administered for five consecutive days, in 21-day cycles. The cost of oral topotecan is £30 per mg, which equates to £69 m^2/day.[51] Each oral capsule contains topotecan hydrochloride equivalent to 0.25 mg or 1 mg of topotecan. The advantage of the oral form of topotecan is that it does not need specialist preparation and administration, and can therefore be self-administered.[52] However, no guidance advising which form may provide the better treatment has been identified.

Treatment may continue until disease progression if the treatment is well tolerated. Oral topotecan can be self-administered on an outpatient basis. IV topotecan is administered in secondary or tertiary care settings, usually on a day case basis.

Topotecan is contraindicated in patients who have a history of hypersensitivity to the active substance, are breast feeding or already have severe bone marrow depression prior to starting first course. Haematological toxicity may occur and a full blood count including platelets should be monitored regularly. As with other anti-cancer therapies, topotecan can cause severe myelosuppression which can lead to sepsis. Other potential adverse effects include nausea and vomiting, diarrhoea, alopecia and fatigue. Topotecan rarely causes life-threatening neutropenic colitis. Topotecan is produced by GlaxoSmithKline and trades under the name 'Hycamtin'.

2 METHODS

The *a priori* methods for systematically reviewing the evidence of clinical- and cost-effectiveness are described in the research protocol (Appendix 2), which was sent to experts for comment. No comments were received which identified specific problems with the methods of the review. The methods outlined in the protocol are briefly summarised below. The methods of the SHTAC economic evaluation can be seen in Section 4.1.

2.1 Search strategy

The search strategy was developed, tested and refined by an experienced information scientist. Separate searches were conducted to identify studies of clinical-effectiveness, cost-effectiveness, QoL, resource use/costs and epidemiology/natural history. Sources of information and search terms are provided in Appendix 3.

Searches for clinical and cost effectiveness literature were undertaken from 1990 to August 2008. Given that marketing authorisation for topotecan was first granted in 1996, it was deemed unlikely that there would be any trials before 1990 for topotecan for any indication. Electronic databases searched included the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); PreMedline In-Process & Other Non-Indexed Citations; Web of Knowledge Science Citation Index (SCI); Web of Knowledge ISI Proceedings; PsychInfo (Ebsco); Biosis; Cinahl (Ebsco); NIHR-Clinical Research Network Portfolio, Current Controlled Trials, Clinical Trials.gov and Cancer Research UK trials. Key cancer resources including the American Society of Clinical Oncology (ASCO) and relevant cancer symposia including the 12th World Lung Cancer Conference were also searched. Updated searches were carried out in February 2009.

The searches were restricted to English language. Bibliographies of related papers were screened for relevant studies, and the manufacturer's submission (MS) to NICE were assessed for any additional studies (see Appendix 4 for a critique of the clinical effectiveness section of the MS, and Section 4.1 for further discussion of the cost-effectiveness section). Experts who were contacted for advice and peer review were also asked to identify additional published and unpublished references. The authors of the five included studies were contacted to establish whether the patient populations in the trials met the review inclusion criteria with regard to being innapropriate for re-treatment with first-line therapy.

2.2 Inclusion and data extraction process

Titles and abstracts identified by the search strategy for the clinical effectiveness section of the review were assessed for possible eligibility by two independent reviewers. The full texts of relevant papers were then obtained and inclusion criteria were applied by one reviewer and checked by a second reviewer. Any disagreements over eligibility were resolved by consensus or by recourse to a third reviewer. Data were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer.

Titles and abstracts identified by the search strategy for the cost effectiveness section of the review were assessed for potential eligibility by two health economists. Economic evaluations were considered for inclusion if they reported both health service costs and effectiveness, or presented a systematic review of such evaluations. Full papers were formally assessed for inclusion by one health economist.

2.2.1 Quality assessment

The quality of included RCTs and systematic reviews was assessed using criteria recommended by the Centre for Reviews and Dissemination (CRD)[53] (Appendix 5). Quality criteria were applied by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion or consultation with a third reviewer.

2.2.2 Inclusion criteria

Population

- Adults (≥18 years) with relapsed SCLC who responded to first-line treatment and for whom re-treatment with first-line therapy is not considered appropriate (due to contraindications, adverse effects).
- Patients may have had limited stage disease or extensive stage disease.

- Response to initial treatment may have been either complete response (CR) or partial response (PR).
- Patients who did not respond to first-line therapy (including patients whose tumours did not respond, or who progressed, during first-line treatment) were not included.
- Studies with a mix of untreated and previously treated patients (or responders and non-responders) were not included unless the groups were reported separately.

Intervention

- Intravenous topotecan (administered as second-line treatment)
- Oral topotecan (administered as second-line treatment)
- Studies with a focus on first-line treatment were not included
- Effectiveness data for oral and intravenous topotecan were not combined.

Comparators

- Intravenous and oral topotecan compared with each other
- BSC (including radiotherapy)
- CAV (cyclophosphamide, doxorubicin, vincristine)
- Other chemotherapy regimens

Outcomes

Studies reporting one or more of the following outcomes were included:

- Time to disease progression
- Progression-free survival
- Response rate (see below)
- Response duration
- Overall survival
- Symptom control
- Health-related QoL (using a validated measure)
- Cost-effectiveness (incremental cost per life year gained) or cost-utility (incremental cost per quality adjusted life year gained)

Adverse effects of treatments were reported if available within trials that met the prespecified inclusion criteria above.

Understanding the definition of treatment 'response' used within the studies is important. Two criteria have been identified which appear to be widely reported in oncology research, the WHO criteria[54] and the RECIST guidelines.[55] These are summarised in Appendix 1. Where a clinical trial documents

which criteria were used to define treatment response and related outcomes, this is reported in the current review. Where it is not certain what the definition of response was this is similarly noted.

Types of studies

RCTs were included. Studies published as abstracts or conference presentations were only included if sufficient details were presented to allow an appraisal of the methodology and the assessment of results to be undertaken. Systematic reviews were used only as a source of references.

For the systematic review of cost-effectiveness, studies were only eligible for inclusion if they reported the results of full economic evaluations (cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses).

2.3 Data synthesis

Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in Appendix 6. It was not considered appropriate to combine the included RCTs in a meta-analysis, due to clinical heterogeneity in the patient groups and comparator treatments.

3 CLINICAL EFFECTIVENESS

3.1 Results

3.1.1 Quantity and quality of research available

Included Studies

Searches identified 395 references, after removal of duplicates. After initial screening of titles and abstracts, 385 references were excluded. Ten full copies of articles were retrieved, with four excluded on further inspection. In addition, 22 abstracts were identified on searches of the proceedings of the American Society of Clinical Oncology (ASCO), with 21 of these being excluded during the screening process. The included ASCO abstract later became available as a fully published article. Two (of nine) abstracts were also identified from the 12th World Lung Cancer Conference 2007, which were linked to one of the included studies. Eight studies were identified in the updated searches, but none were included. The total number of published papers included at each stage of the systematic review is shown in the flow chart in Figure 9 (in Appendix 3); the list of excluded studies can be seen in Appendix 7.

Ten publications describing five RCTs appeared to meet the inclusion criteria of the review.[56-65] Five of the articles were either earlier abstracts[60-62] or abstracts presenting additional results[64,65] linked to

full publications,[56,57,59,63] leaving five RCTs to be evaluated. Only one trial appeared to fully meet the inclusion criteria of the review on inspection of the published article,[57] and this was confirmed in correspondence with the author (participants were inappropriate for re-treatment with their original first-line chemotherapy for reasons such as contraindication, toxicity and refusal). The remaining four RCTs did not appear to fully meet the inclusion criteria of having participants for whom re-treatment with their first-line chemotherapy regimen was not appropriate, as per the licensed indication for topotecan. Authors of all of these publications were contacted to clarify this aspect of our inclusion criteria. Response from one author established that two of the included trials[58,59] did meet this aspect of the inclusion criteria. In the correspondence with the author from a third trial,[63] it was reported that participants were not required to have a 'contraindication' to re-treatment with their first-line therapy to meet the study protocol. Whether there were other reasons that would have deemed participants as being inappropriate for re-treatment, or whether all participants could have been appropriate for re-treatment is however not clear. No reply was received from the author of one other study,[56] so it remains unclear whether the included participants fully met the licensed indication for topotecan. Despite these uncertainties, these latter two studies were included, although we emphasise the need for caution in the interpretation of results as the population groups may be slightly different than those eligible for topotecan according to the marketing authorisation. In summary, five trials were included in this review (see Table 1).

Table 1 Studies included in the review, by intervention

Study	Intervention	Comparator
O'Brien *et al.* 2006[57,64,65]	Oral topotecan + BSC	BSC alone
von Pawel *et al.* 1999[59,61]	IV topotecan	CAV
Eckardt *et al.*2007[56,60]	Oral topotecan	IV topotecan
von Pawel *et al.* 2001[58]	Oral topotecan	IV topotecan
Inoue *et al.* 2008[62,63]	IV topotecan	IV amrubicin

3.1.2 Description of the included studies

Four[56-59] of the included studies were international, multi-centre RCTs, varying between 31 to 83 centres (numbers not reported in one[59]). The fifth study[63] was a multi-centre RCT carried out in 12 centres in Japan. Two of the studies were phase II trials.[58,63] Four of the trials were sponsored by the drug manufacturers,[56-59] whilst financial support was reported to be provided by two of the authors in the trial by Inoue and colleagues.[63]

The O'Brien and colleagues (2006)[57] study investigated oral topotecan and BSC versus BSC alone in a population of participants considered unsuitable for further IV chemotherapy. The study initially excluded participants with a treatment-free interval (TFI) of > 90 days for whom treatment with BSC

was not acceptable. This changed during the trial and some participants with sensitive SCLC, who were unsuitable for standard chemotherapy due to co-morbidities or who had refused chemotherapy due to the risk of toxicity, became eligible for inclusion in the study. In the topotecan and BSC group, participants received 2.3 mg/m^2 of oral topotecan on day one to five every 21 days. A minimum of four treatment cycles were recommended, but delays and dose adjustments were anticipated in the study protocol. BSC was defined as including measures such as "analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, red blood cell transfusions, deep relaxation therapy, and palliative radiotherapy or surgical procedures". Both treatment groups had equal access to these treatments.

A study by von Pawel and colleagues (1999)[59] compared intravenous topotecan against CAV (cyclophosphamide, doxorubicin and vincristine), in a population of participants with limited- or extensive-stage SCLC, with a CR or PR to first-line chemotherapy and who had relapsed ≥ 60 days after cessation of first-line therapy. Participants who were contraindicated to retreatment with CAV were specifically excluded from this study and therefore the participants may not be those that would normally be eligible for topotecan. The intravenous topotecan group received 1.5 mg/m^2 as a 30 minute infusion for five days every 21 days, while the CAV group received an infusion of 1000 mg/m^2 (max. 2000mg) of cyclophosphamide, 45 mg/m^2 (max. 100mg) of doxorubicin and 2 mg of vincristine all on day one of each 21-day course. Participants with stable disease received a minimum of four treatment cycles, whilst patients with a CR or PR received at least six.

Two studies[56,58] compared oral topotecan with intravenous topotecan, in a population of participants with limited- or extensive-stage relapsed SCLC who had CR or PR to first-line therapy with disease recurrence after≥ 90 days. In both studies, participants received 2.3 mg/m^2 of oral topotecan compared to 1.5 mg/m^2 of intravenous topotecan for five days every 21 days. Treatment duration depended on response, but in both studies participants with stable disease received at least four treatment cycles. Protocol-specified dose adjustments were permitted in both trials.

The trial by Inoue and colleagues[63] compared intravenous topotecan with intravenous amrubicin (an anthracycline) in a population of SCLC participants previously treated with platinum-containing chemotherapy and who had either sensitive (relapse ≥ 90 days after cessation of first-line therapy) or refractory relapse (relapse within 90 days after cessation of first-line therapy). The study suggested that the latter category may also include participants who never responded to first-line treatment, although whether this is the case or what proportion this includes is unknown. The majority of participants were sensitive to the first-line therapy. Participants received 40 mg/m^2 of amrubicin as a five-minute infusion on days one to three every three weeks. Topotecan was administered as a 30-minute infusion on days one to five every three weeks at a dose of 1.0 mg/m^2, which is the approved

dosage in Japan. This is lower than the UK recommended dose (1.5 mg/m^2/d) given in the other studies.[56,58,59]

The key characteristics of the RCTs are shown in Table 2. The mean age of the participants in four of the studies was similar (58-70 years), while the fifth study provided no information about the age of the participants.[59] All studies had a higher percentage of male participants in both treatment arms (male range 57% to 83%: female range 17% to 43%). Where reported, studies had a higher proportion of participants with extensive-stage disease and these were comparable across treatment groups. The percentage of participants with extensive disease was similar in three studies[56-58] at 61-72%, higher in a fourth study[59] at 83-85%, and not reported by the fifth study.[63]

The proportion of participants with a performance status of zero was lowest in the O'Brien and colleagues study[57] (~10%), higher in three trials,[56,58,59] ranging from 17-33%, whilst the trial by Inoue and colleagues[63] had a much higher proportion (48-57%). Four trials had similar proportions of participants (55-65%) with a performance status of one,[56-59] with the exception of the IV topotecan group in the von Pawel and colleagues (2001) trial[58], which was lower (39%). This was similar to the proportions in both treatment groups (30-34%) in the study by Inoue and colleagues (2008).[63] When grouping together performance status zero and one, all trials had similar numbers of good performance status participants (70-80%). The percentage of participants with a performance status of two were mixed between studies. Within two studies,[56,63] the proportion was low and similar across arms (12-17%). In a third study,[59] percentages were slightly higher (19-24%), and in a fourth trial[57] percentages were higher still (27-33%), but similar across treatment arms. In the trial by von Pawel and colleagues (2001),[58] there were almost twice as many participants with a performance status of two in the intravenous topotecan group (28%) compared to the oral topotecan group (15%).

Liver metastases were present in around 30% of participants in two studies,[56,58] but higher in both treatment groups (~40%) in the study by von Pawel and colleagues (1999).[59] In the O'Brien and colleagues' study,[57] liver metastases were present in a greater proportion of topotecan participants (28%) compared to BSC (20%), although the authors do not report that this is a statistically significant difference. Presence of liver metastases was not reported in the trial by Inoue and colleagues.[63] Duration of response to first-line chemotherapy was six months or more for the majority of patients in both treatment groups for two studies,[56,58] and around a median of 23-24 weeks in another study.[59] Inoue and colleagues[63] did not report this data. In the study by O'Brien and colleagues,[57] this was reported as median time to progression after first-line chemotherapy, and was 84 days in the topotecan arm and 90 days in the BSC arm.

Four RCTs[56,58,59,63] reported response rate as the primary outcome measure, with the two trials by von Pawel and colleagues also reporting duration of response[58,59] and time to progression.[58] Overall survival and toxicities/symptoms were reported as secondary outcomes in these four studies. O'Brien and colleagues[57] reported overall survival as the primary outcome and response rate, time to disease progression and adverse effects/toxicities as secondary outcome measures. Two trials[56,57] reported health-related QoL.

Table 2 Characteristics of included studies

Study details	Interventions	Key inclusion criteria and patient characteristics	Outcomes
O'Brien *et al.*, 2006;[57] Chen *et al.*, 2007[64] (abstract) and O'Brien *et al.*, 2007[65] (abstract) *Study design:* RCT *Countries:* Europe, Canada and Russia *Number of centres:* 40 *Sponsor:* GSK *Follow-up:* Median time on study 7.8 weeks in the BSC group and 12.3 weeks in the topotecan group.	1. Oral topotecan and BSC, 2.3 mg/m^2/day on days 1 to 5 every 21 days (n= 71). 2. BSC (n=70)	*Target population*: only those considered unsuitable for further IV chemotherapy were recruited. *Inclusion criteria* - extensive or limited SCLC, resistant or sensitive disease, one prior chemotherapy regimen, age ≥18 years, ECOG PS of 0, 1 or 2, at least 24 hours since last radiotherapy, at least 3 months since last immunotherapy. *Gender (M/F), n (%):* topotecan 52/19 (73/27); BSC 51/19 (73/27) *Mean age (SD), range, years*: topotecan 59.8 (9.0) 37-76; BSC 58.6 (8.2), 43-79 *Performance status, n (%):* 0: topotecan 8 (11%); BSC 6 (9%) 1: topotecan 44 (62%); BSC 41 (59%) 2: topotecan 19 (27%); BSC 23 (33%) *Disease stage, n (%)*: Limited: topotecan 23 (32%); BSC 27 (39%) Extensive: topotecan 48 (68%), BSC 43 (61%) *Previous treatment:* Any prior treatment: topotecan 46 (65%); BSC 48 (69%) Radiotherapy: topotecan 38 (54%); BSC 34 (49%) Surgery: topotecan 18 (25%); BSC 20 (29%) Immunotherapy: topotecan 0; BSC 4 (6%) Cisplatin or carboplatin: topotecan 80%, BSC 77% Etoposide: topotecan 76%; BSC 74% *Duration of response to 1st-line chemotherapy:* (time to progression since completion of 1st-line therapy), days, n (%): ≤ 60: topotecan 22 (31%); BSC 20 (29%) > 60: topotecan 49 (69%); BSC 50 (71%) ≤ 90: topotecan 41 (58%); BSC 35 (50%) >90: topotecan 30 (42%); BSC 35 (50%) *Presence of liver metastases, n (%):*	*Primary outcomes*: Overall survival. *Secondary outcomes*: Response rate, time to disease progression (TTP), Patient Symptom Assessment (PSA), QoL and safety.

		Present: topotecan 20 (28%), BSC 14 (20%) Absent:topotecan 51 (72%); BSC 56 (80%)	
von Pawel *et al.*, 1999[59] and Schiller *et al.*,1998[61] (abstract) *Study design:* RCT *Countries:* Germany, Canada, France, UK and USA *Number of centres:* not reported *Sponsor:* SmithKline Beecham *Follow-up*: unclear, although the range for time to progression was 75 weeks and for survival up to 101 weeks	1. Topotecan, 1.5 mg/m^2/d as 30 min. infusion for 5 days every 21 days (n=107) 2. CAV (cyclophosphamide, doxorubicin and vincristine),C 1000 mg/m^2 (max. 2000 mg), D 45 mg/m^2 (max. 100 mg), and V 2 mg infusion all on day 1 of each 21-day course (n=104) Minimum 4 courses of treatment for patients with stable disease, ≥ 6 courses for patients with CR or PR.	*Target population:* patients with progressive, limited or extensive-stage SCLC, with date of progression ≥60 days after completion of 1st-line therapy. *Inclusion criteria:* One previous chemotherapy regimen, at least 1 lesion bi-dimensionally measurable; ≥4 weeks between prior surgery or immunotherapy and study entry; ≥ 24 hours between radiotherapy and initiation of study drugs; ECOG PS ≤ 2. *Gender (M/F), n (%)*: T 61/46 (57/43), CAV 71/33 (68/32) *Mean age*: not reported *Performance status, n (%)*: 0: T 18 (16.8%); CAV 20 (19.2%) 1: T 64 (59.8%); CAV 64 (61.5%) 2: T 25 (23.4%); CAV 20 (19.2%) *Disease stage, n (%)*: Limited: T 18 (16.8%); CAV 16 (15.4%) Extensive: T 89 (83.2%); CAV 88 (84.6%) *Duration of response to 1st-line chemotherapy, median weeks (range)*: T 24.4 (7.6-430.6); CAV 22.9 (8.7-156.7) *Presence of liver metastases, n (%)*: Present: T 43 (40.2%), CAV 42 (40.4%) Absent: T 64 (59.8%), CAV 62 (59.6%)	*Primary outcomes:* Response rate and duration to response. *Secondary outcomes:* Time to progression, time to response, survival and improvement of disease-related symptoms.
Eckardt *et al.*, 2007[56] and Eckardt *et al.*, 2003[60] (abstract) *Study design:* Open-label RCT *Countries:* Europe, N. America, S.E. Asia and Australia	1. Oral topotecan, 2.3 mg/m^2/day on days 1-5 every 21 days (n= 155) 2. I.V. topotecan, 1.5 mg/m^2/day, on days 1-5 every 21 days (n=154) Duration depended on	*Target population*: patients with limited- or extensive-stage relapsed SCLC who had CR or PR to 1st line therapy with disease recurrence after ≥ 90 days. *Inclusion criteria:* ≥ 18 years, only 1 prior chemotherapy regimen, bi-dimensionally measurable disease (according to WHO criteria), ECOG PS ≤ 2, prior surgery was allowed if ≥ 4 weeks had passed, as was immunotherapy (≥ 3 months) and radiotherapy (≥ 24 hours). *Gender (M/F), n (%)*: oral 98/55 (64.1/35.9), IV 96/55 (63.6/36.4) *Mean age (range), years:* oral 62.5 (41-82), IV 62.0 (35-82)	*Primary outcomes:* Response rate. *Secondary outcomes:* Time to response, response duration, time to disease progression, overall survival, toxicities and HR-QoL.

Number of centres: 83 *Sponsor:* GSK *Follow-up*: Median of 4 courses (i.e. 12 weeks); at least 40% of patients in each group received treatment beyond course 4.	response but those with stable disease recommended to have at least 4 cycles. NB: Baseline characteristics and results based on n=153 oral and n=151 IV participants who received at least one treatment.	*Performance status, n (%):* 0: oral 48 (31.4%), IV 35 (23.2%) 1: oral 85 (55.6%), IV 98 (64.9%) 2: oral 20 (13.1%), IV 18 (11.9%) *Disease stage, n (%):* Limited: oral 51 (33.3%), IV 45 (29.8%) Extensive: oral 102 (66.7%), IV 106 (70.2%) *Previous treatment*: platinum-based and anthracycline-based combination regimens. *Duration of response to 1st-line chemotherapy, n (%)* (data missing for 4 patients in the oral group and 1 pt in the IV group)*:* < 3 months: oral 15 (9.8%), IV 13 (8.6%) 3-6 months: oral 50 (32.7%), IV 54 (35.8%) > 6 months: oral 84 (54.9%), IV 83 (55.0%) *Presence of liver metastases, n (%):* Present: oral 44 (28.8%), IV 43 (28.5%) Absent: oral 109 (71.2%), IV 108 (71.5%)	
von Pawel *et al.*, 2001[58] *Study design:* RCT (phase II) *Countries:* Europe, S. Africa and Australia *Number of centres:* 31 *Sponsor:* SmithKline Beecham *Follow-up*: unclear, although progression was assessed up to 54 weeks and survival up to 64 weeks.	1. Oral topotecan, 2.3 mg/m^2/d for 5 days every 21 days (n=52) 2. IV topotecan, 1.5 mg/m^2/d, 30 min infusion for 5 days every 21 days (n=54) Duration depended on response but those with stable disease recommended to have at least 4 cycles.	*Target population:* patients with limited- or extensive-stage SCLC, with a CR or PR to 1st-line chemotherapy and who had relapsed ≥ 3 months after cessation of 1st-line therapy. *Inclusion criteria:* ≥ 18 years, only one prior chemotherapy regimen, measurable disease of ≥ 2cm in diameter, WHO performance status of ≤ 2, life expectancy of at least 2 months, ≥ 4 weeks since previous surgery and ≥ 24 hours since last radiotherapy. *Gender (M/F), n (%)*: Oral 39/13 (75/25), IV 43/11 (79.6/20.4) *Mean age (range), years:* Oral 59.9 (38-79), IV 58.2 (35-74) *Performance status, n (%)*: 0: Oral 10 (19.2%); IV 18 (33.3%) 1: Oral 34 (65.4%); IV 21 (38.9%) 2: Oral 8 (15.4%); IV 15 (27.8%) *Disease stage, n (%)* (data missing for 1 pt in each group): Limited: Oral 14 (26.9%); IV 14 (25.9%)	*Primary outcomes:* Response, response duration, time to progression. *Secondary outcomes:* Time to response, survival, symptoms and toxicities.

		Extensive: Oral 37 (71.2%); IV 39 (72.2%) *Previous treatment*: Previous radiotherapy (%): Oral 71.2%, IV 72.2% *Duration of response to 1st-line chemotherapy, n (%)*: Time to disease progression since completion of 1st-line therapy: < 3 months*: Oral 1 (1.9%); IV 1 (1.8%) 3-6 months: Oral 19 (36.5%); IV 19 (35.2%) > 6 months: Oral 32 (61.5%): IV 34 (63.0%) * treatment free interval of 11 weeks and 11.7 weeks *Presence of liver metastases, n (%)*: Present: Oral 16 (30.8%); 17 (31.5%) Absent: Oral 36 (69.2%); IV 37 (68.5%)	
Inoue *et al*., 2008[63] and Sugawara *et al.*, 2008[62] (abstract and presentation) *Study design:* RCT (phase II) *Countries:* Japan *Number of centres:* 12 *Sponsor:* 2 authors provided financial support. *Follow-up*: not stated.	1. Intravenous amrubicin (A), 40mg/m^2/d on days 1-3 every 3 weeks (n=29*) 2. Intravenous topotecan (T), 1.0mg/m^2/d on days 1-5 every 3 weeks (n=30) At least 3 cycles (A: median 3, range 1-7; T: median 2, range 1-4) *A: 1 patient was not treated due to rapid disease progression	*Target population:* previously platinum-treated SCLC patients who relapsed within 90 days or ≥90 days after cessation of 1st-line treatment. NB: some participants may have never responded to 1st-line therapy. *Inclusion criteria*: Age ≥20 years, 1 platinum-containing previous chemotherapy regimen, measurable disease with RECIST criteria, no chemotherapy or chest radiotherapy within 4 weeks prior to enrolment, ECOG PS of 0-2. *Gender (M/F), n (%)*: A 24/5 (83/17); T 25/5 (83/17), *p*=1.000 *Age (years), median (range):* A 70 (54-77); T 64 (32-78), *p*=0.195 *Performance status, n (%)*: 0: A 14 (48%); T 17 (57%) 1: A 10 (34%); T 9 (30%) 2: A: 5 (17%); 4 (13%), *p*=0.731 *Disease stage*: not reported *Duration of response to 1st-line chemotherapy*: not reported Presence of liver metastases, n (%): not reported *Previous treatment, n (%)*:	*Primary outcomes:* Overall response rate (ORR). *Secondary outcomes:* Progression free survival (PFS), overall survival (OS) and toxicity profile. Also reports disease control rates, but data not extracted.

		Radiotherapy: A 15 (52%); T 16 (53%) Chemotherapy: Platinum + etoposide: A 22 (76%); T 20* (67%) Platinum + irinotecan: A 7 (24%); T 11* (37%) *1 pt received 1st line treatment with platinum etoposide and irinotecan *Response type, n (%)*: Sensitive: A 17 (59%); T 19 (63%) Refractory: A 12 (41%); T 11 (37%), *p*=0.793	

Quality assessment of included studies

The methodological quality of reporting in the included studies was assessed using criteria set by CRD at the University of York,[53] and varied across studies (see Table 3). Two trials[57,59] described an adequate randomisation procedure which ensured both true random assignment to treatment groups and adequate concealment of allocation. The other three studies[56,58,63] provided no details of the methods of generating the randomisation sequence nor the allocation procedure used, and consequently are rated as unknown on these quality factors. Without adequate published information, it is not possible to assess whether there is a risk of selection bias in these studies, with the allocation sequence being open to possible manipulation.

All the trials reported eligibility criteria adequately and participants appeared similar at baseline on key demographic and prognostic characteristics, although in some cases supporting statistical comparisons were not provided. None of the RCTs reported if either the care givers or participants were blinded to the treatment. However, given the disparity in the treatment interventions, blinding of participants or care providers may have not been possible in some trials, but the studies did not discuss this. Details of blinding for outcome assessors were partially reported by three trials,[56,58,59] inadequately reported in one trial[57] and unknown in one trial.[63] This may lead to detection bias, particularly for subjective outcomes such as QoL assessments. Outcomes were reported adequately in four trials,[56-59] and partially in one.[63] In only three trials was an appropriate intention to treat (ITT) data analysis reported to be undertaken and assessed as adequate.[57-59] In two trials,[56,63] the analysis was not true ITT, as it was based on all those who received treatment, not on all those who were randomised. Reasons for withdrawals were adequately explained by three trials,[56,57,63] partially reported by one[59] and classed inadequate for another trial as there was no discussion of numbers or reasons for any attrition.[58] Overall, methodological quality was judged to be reasonably good in two trials, and unknown in three trials.

Table 3 Quality assessment of included trials

Study	Randomisation	Allocation concealment	Baseline characteristics	Eligibility	Blinding of assessors	Blinding of care providers	Patient blinding	Reporting outcomes	Intention-to-treat analysis	Withdrawals explained
Eckardt *et al.*2007[56,60]	Un	Un	Rep	Ad	Par	Un	Un	Ad	In	Ad
Inoue *et al.*2008[62,63]	Un	Un	Rep	Ad	Un	Un	Un	Par	In	Ad
O'Brien *et al.*2006[57]	Ad	Ad	Rep	Ad	In	Un	Un	Ad	Ad	Ad
von Pawel *et al.*1999[59,61]	Ad	Ad	Rep	Ad	Par	Un	Un	Ad	Ad	Par
von Pawel *et al.*2001[58]	Un	Un	Rep	Ad	Par	Un	Un	Ad	Ad	In

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

3.1.3 Assessment of clinical effectiveness

3.1.3.1 Topotecan and BSC versus BSC

Survival

One trial (O'Brien and colleagues[57]) was included which compared topotecan plus BSC with BSC alone. Overall survival was the primary outcome in this study. The median survival was reported to be 25.9 (95% CI 18.3, 31.6) weeks in the topotecan plus BSC treated participants and 13.9 (95% CI 11.1, 18.6) weeks in those with BSC alone. This was not tested for statistical significance. Six month survival rates were 49% versus 26% for the topotecan plus BSC and BSC groups respectively (Table 4). Using Kaplan-Meier analysis, the hazard ratio for overall survival was 0.64 (95% CI 0.45, 0.90) in favour of topotecan. With adjustment for covariates, the hazard ratio was reported to be 0.61 (95% CI 0.43, 0.87). This showed a statistically significant benefit for the topotecan plus BSC group compared to BSC alone (log-rank p=0.01).

Data were presented on subgroup analyses of survival according to the various stratification factors (gender, performance status, time to progression (TTP), presence of liver metastases). However, the hazard ratios and 95% confidence intervals (CI) were only presented in a figure and hence are not reported in detail here. Estimates of these rates can be seen however in Appendix 6. Overall, the data indicate a survival trend favouring topotecan plus BSC for all subgroups analysed. However, the 95% CI cross 1.0 for TTP > 60 days, male gender, PS 0/1, and liver metastases on the figures presented in the paper. It is also not clear whether the study was powered for these analyses.

Participant drop out rates differed between the study arms (30% topotecan + BSC, 47% BSC) although the study reports that an ITT principle to the analyses of data was applied. No participants crossed over, although there were a number of participants in both groups who received additional chemotherapy and/or radiotherapy post-study. It is not clear whether this may have had an impact on the overall survival rates shown, but the proportions receiving post study chemotherapy are observed to be similar between treatment arms (18.6% and 18.3% for the topotecan + BSC and BSC arms respectively).

Table 4 Overall survival (topotecan + BSC versus BSC)

Study	**Treatment arms**		**p-value**
O'Brien *et al.*, 2006[57]	Topotecan + BSC (n=71)	BSC (n=70)	
Overall survival, median (weeks)	25.9 (95% CI 18.3, 31.6)	13.9 (95% CI 11.1,18.6)	Not reported
Six-month survival rate	49%	26%	Not reported

Progression free survival was not reported in the O'Brien and colleagues[57] study.

Response

The overall response rate, (classified as either complete or partial response, although only partial responses were seen) was measured in 60 of the 71 participants randomised to topotecan plus BSC. This was measured using WHO criteria and was reported to be seven percent (95% CI 2.33, 15.67). The study also reports a sub-group analysis according to one stratification factor (TTP) for response, but this data are not reported here as it was for the topotecan plus BSC group only.

Duration of response

The median time to progressive disease in the topotecan plus BSC group was 16.3 weeks (95% CI 12.9, 20.0). Those in the BSC group were already in a progressive disease state and hence no comparison was made in the study report. It was also reported that 83% (n=59) of the topotecan plus BSC group experienced progression and 34% (n=24) reached progressive disease (by WHO criteria). Some 44% (n=31) of participants had achieved stable disease. It is unclear in the study report at what point this data were collected.

Quality of life

The O'Brien and colleagues[57] study reports the rate of deterioration of QoL (per 3-month period) as measured by the EQ-5D (lower score indicates worse QoL). Baseline EQ-5D questionnaires were completed by 68 (96%) participants in the topotecan plus BSC group and 65 (93%) participants in the BSC group. At least one post-baseline questionnaire was completed by 63 (89%) participants in the topotecan plus BSC group and 49 (70%) participants in the BSC group. No baseline scores were presented (see Appendix 11). The results showed a difference between treatment arms favouring the topotecan plus BSC arm (topotecan + BSC: -0.05, 95% CI -0.11, 0.02, BSC: -0.20, 95% CI -0.27, -0.12, difference 0.15, 95% CI 0.05, 0.25).

The Chen and colleagues (2007)[64] abstract reported additional QoL data on the EQ-5D index as well as the Visual Analogue Scale (VAS; lower score indicates poorer imaginable health state). The mean change from baseline in both the EQ-5D index and VAS for the pooled and last evaluation analyses was statistically significantly different between groups (Table 5), indicating a smaller decline in health status for those receiving topotecan and BSC. It should be noted that the high proportion of participants reported to have completed at least one post-baseline questionnaire does not necessarily reflect the number of participants in the pooled and last evaluation analyses. In the pooled estimate, there will be a number of participants who were tested a number of times (depending on, for example, survival, inability or refusal to complete the questionnaire) with the results of multiple assessments averaged; in the last evaluation analysis, it is possible that results from some participants were missing for the same reasons, but these numbers are not known. Also caution should be taken in interpreting the results as the data are reported in abstract form only.

Table 5 Quality of life (topotecan + BSC versus BSC)

Study	**Treatment arms**		**p-value**
O'Brien *et al.*, 2006[57,64]	Topotecan + BSC (n=71)	BSC (n=70)	
EQ-5D, rate of deterioration per 3 month interval	-0.05 (95% CI -0.11, 0.02)	-0.20 (95% CI -0.27, -0.12)	Difference 0.15 (95% CI 0.05, 0.25)
EQ-5D Index (pooled analysis†), mean change from baseline	-0.03	-0.12	Difference 0.09 p=0.0036
EQ-5D Index (change*), mean change from baseline	-0.10	-0.30	Difference 0.2 p=0.0034
EQ-5D VAS (pooled analysis†), mean change from baseline	0.30	-7.41	Difference 7.71 p<0.0001
EQ-5D VAS (change*), mean change from baseline	-3.98	-14.46	Difference 10.48 p=0.0025

†change from baseline to averaged on-treatment assessments; *change from baseline to last evaluation analysis.

Symptoms

O'Brien and colleagues[57] also report participant symptoms based on a self-reported measure, the Patient Symptom Assessment (PSA) scale, which evaluates the degree to which participants experience nine symptoms, rating from 1 (no symptom) to 4 (very severe symptoms). The results are presented as odds ratios (OR) of the likelihood of symptom improvement with topotecan plus BSC relative to BSC alone. The ORs presented for each individual symptom suggest that shortness of breath (OR 2.18, 95% CI 1.09, 4.38), sleep disturbance (OR 2.16, 95% CI 1.15, 4.06) and fatigue (OR 2.29, 95% CI 1.25, 4.19) are likely to be statistically significantly improved in those with topotecan and BSC (all $p<0.05$). The other symptoms were not found to be statistically significantly different between the two treatment arms (individual symptoms can be seen in Table 6). For this measure, baseline questionnaires were completed by 70 participants in the topotecan plus BSC group and 67 participants in the BSC group. The numbers of participants with sufficient data to be included in the analyses varied for the symptom scores between 47-48 for the BSC group and 60-61 for the topotecan plus BSC group. In addition, while this scale is reported to resemble a well-validated Lung Cancer Symptom Scale, it is unclear whether the PSA scale has been validated, therefore the outcomes should be cautiously interpreted. A more recent abstract (2007) by O'Brien and colleagues[65] presents a sub-group analysis of the association between baseline PSA total scores and performance status according to partial response or stable disease for the topotecan plus BSC group only, but the data have not been extracted nor reported here.

Table 6 Symptoms (topotecan + BSC versus BSC)

Study	Odds ratio topotecan : BSC	95% CI	p-value
O'Brien *et al.*, 2006[57]			
Improvement in PSA scores:			
Shortness breath	2.18	1.09, 4.38	p<0.05
Cough	1.35	0.68, 2.66	ns
Chest pain	2.07	1.00, 4.28	ns
Coughing blood	1.95	0.46, 8.27	ns
Loss of appetite	1.02	0.57, 1.84	ns
Interference sleep	2.16	1.15, 4.06	p<0.05
Hoarseness	1.35	0.63, 2.87	ns
Fatigue	2.29	1.25, 4.19	p<0.05
Interference with daily activity	1.70	0.95, 3.03	ns

Adverse events and toxicity

Rates of adverse events between those in the topotecan plus BSC arm and those in the BSC alone arm were reported for non-sepsis infection, sepsis, diarrhoea, fatigue, vomiting, dyspnoea and cough in the O'Brien and colleagues study[57] and can be seen in Table 7. From this it can be observed that rates were generally low and similar across groups, with the exception of diarrhoea and dyspnoea which are slightly different between groups. None of these were tested for statistical significance. All cause mortality within 30 days of randomisation was 7% in the topotecan plus BSC arm and 13% in the BSC alone arm.

Table 7 Adverse events (topotecan plus BSC versus BSC)

Study	Treatment arms	
O'Brien *et al.*, 2006[57]	Topotecan + BSC (n=71)	BSC (n=70)
Non-sepsis infection ≥ grade 2	10 (14%)	8 (12%)
Sepsis	3 (4%)	1 (1%)
Diarrhoea	6%	0
Fatigue	4%	4%
Vomiting	3%	0
Dyspnoea	3%	9%
Cough	0	2%

Treatment related toxicity was also presented for the topotecan treated group and can be seen in Table 8. From this it can be seen that 61% had grade 3 or 4 neutropenia, with three percent of participants (n= 2) observed to have febrile neutropenia. Grade 3 or 4 thrombocytopenia was seen in 38% of participants, and anaemia in 25%. It is unclear, because of the nature of the study, what the impact of these rates of toxicities may be taken to mean as there can be no comparator data. Toxic deaths occurred in 4 (6%) participants, three of which were due to haematological toxicity.

Table 8 Toxicities (topotecan + BSC versus BSC)

Study	
O'Brien *et al.*, 2006[57]	Topotecan + BSC (n=71)
Treatment related toxicity: Grade 3/4 neutropenia Grade 3/4 thrombocytopenia Grade 3/4 anaemia Febrile neutropenia	 61% 38% 25% 3%

Summary of effectiveness of topotecan plus BSC versus BSC

In this one RCT of reasonable quality, there appears to be an overall survival benefit to having topotecan in addition to BSC. The hazard ratio, adjusted for baseline covariates, was favourable to topotecan and showed a 61% greater chance of survival in the topotecan plus BSC group. Overall survival was the primary outcome in this study. Response was only measured in those in the topotecan group as no comparator was appropriate. In those who were assessed, QoL was better in those given topotecan in addition to BSC. Rates of adverse events appeared to be similar between the two groups. Toxicities were reported, but due to the nature of the comparator intervention cannot be placed into context in this study alone.

3.1.3.2 IV topotecan versus CAV

Survival

The von Pawel and colleagues (1999) trial[59] was the only trial which compared IV topotecan with CAV. The median overall survival was reported to be 25.0 weeks (range 0.4 - 90.7) for topotecan participants and 24.7 weeks (range 1.3 - 101.3) for CAV participants (Table 9). The Cox regression model for survival showed no statistically significant difference between treatment groups (p=0.795), with a risk ratio of topotecan to CAV of 1.039. At the time of analysis, 11.2% and 12.5% of topotecan and CAV participants respectively were censored for survival. The six month and 12 month survival rates, calculated using Kaplan-Meier analysis, were similar between treatment groups and can be seen in Table 9.

Sub-group analyses (see Appendix 6 for full data) of the two stratification factors, baseline performance status and extent of disease, found that these were statistically significant prognostic factors for survival ($p<0.001$). In addition to the stratification factors, gender, baseline liver metastases and baseline brain metastases were also found to be significant factors for survival ($p<0.05$). However, after adjustment for the covariates, the effect of treatment was still not statistically significant (RR 1.17, p=0.322). It should be noted that it is unclear if the study was powered for the sub-group analyses and results should be interpreted with caution.

Progression-free survival was not reported in the von Pawel and colleagues (1999) study.[59]

Table 9 Overall survival (IV topotecan versus CAV)

Study	**Treatment arms**		**p-value**
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)	CAV (n=104)	
Overall survival (weeks) median (range)	25 (0.4 - 90.7)*	24.7 (1.3 - 101.3)	p = 0.795
Survival rate, %: 6 months 12 months	 46.7 14.2	 45.2 14.4	Not reported

*includes censored events

Response

Response rate and duration of response were the primary outcomes in this study, and response rates were determined using the WHO criteria. The overall response rate was 24.3% (95% CI 16.2, 32.4) for participants who received topotecan compared to 18.3% (95% CI 10.8, 25.7) for participants who received CAV (p=0.285), with a difference in the rates of response of 6.0% (95% CI 6, 18) (Table 10). A complete response was achieved in only one participant (CAV); 24.3% and 17.3% of topotecan and CAV participants respectively achieved a partial response. A logistic regression model (evaluating the effect of baseline characteristics) identified presence of baseline liver metastases and gender as significant factors in determining response (p=0.043 and p=0.008 respectively, see Appendix 6). It should be noted that the authors only presented data for the factors which were shown to be statistically significant. After adjusting for the co-variates, it is reported that those treated with topotecan showed a greater propensity to respond than did those treated with CAV, although the result was not statistically significant (OR 1.24, p=0.557). Sub-group analyses for males and females, and for those experiencing relapse 60 to 90 days after completion of first-line chemotherapy, were reported but not tested for statistical significance (see Appendix 6).

Table 10 Response (IV topotecan versus CAV)

Study	**Treatment arms**		**p-value, 95% CI**
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)	CAV (n=104)	
Overall response rate, n (%) -complete response -partial response	26 (24.3) 95% CI 16.2 - 32.4 0 26 (24.3)	19 (18.3) 95% CI 10.8 - 25.7 1 (1) 18 (17.3)	p = 0.285, Difference 6.0% 95% CI 6-18
Response duration (weeks), median (range)	n=26 14.4 (9.4-50.1)	n=19 15.3 (8.6-69.9)*	p = 0.300
Time to response (weeks), median (range)	n=26 6 (2.4 - 15.7)	n=19 6.1 (5.4 - 18.1)	p = 0.953
Non-responders, n (%) -overall -stable disease	 81 (75.7) 21 (19.6)	 85 (81.7) 12 (11.5)	Not reported

-progressive disease -not assessable	49 (45.8) 11 (10.3)	55 (52.9) 18 (17.3)	

*includes censored events

Duration of response and time to response

High proportions of participants in each treatment group did not respond to treatment. The proportion of non-responders reported to have stable or progressive disease (according to WHO criteria) or who were not assessable are shown in Table 10. On the whole, the proportions appear similar between treatment groups although slightly more in the topotecan arm achieved stable disease. However, no statistical comparison was reported. The median duration of response was 14.4 weeks (range 9.4 - 50.1) in the topotecan group and 15.3 weeks (range 8.6 - 69.9) in the CAV group, with no statistically significant difference between groups (p=0.300). Similarly, the median time to response was not statistically different between treatments (p=0.953) and was approximately six weeks in each arm.

Time to progression

No statistically significant difference was found between topotecan and CAV for median time to disease progression (13.3 weeks vs 12.3 weeks respectively, p=0.552) (see Table 11).

Table 11 Time to disease progression (IV topotecan versus CAV)

Study	**Treatment arms**		**p-value**
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)	CAV (n=104)	
Time to progression (weeks), median (range)	13.3 (0.4 - 55.1)	12.3 (0.1 - 75.3)*	p = 0.552

*includes censored events

Quality of life

QoL was not reported in the von Pawel and colleagues (1999) study.[59]

Symptoms

von Pawel and colleagues (1999)[59] used a symptom-specific SCLC questionnaire to measure participant symptoms. Patient symptom assessments were scored on a four-point ordinal scale (1, not at all; 2, a little bit; 3, quite a bit; 4, very much), and improvement had to be two consecutive improvements over the baseline assessment. Symptom evaluation also included the time to symptom worsening as defined by the interval from the first dose of study medication until the first evidence of worsening in the post-baseline assessment.

Using Pearson's uncorrected Chi square statistic to compare treatment groups, greater symptomatic improvement was seen in participants who received topotecan for symptoms of dyspnoea (p=0.002), anorexia (p=0.042), hoarseness (p=0.043) and fatigue (p=0.032), as well as for interference with daily

activity (p=0.023). The other symptoms (see Table 12) were not found to be statistically significantly different between the two treatment arms. For this measure, the number of participants with sufficient data to be included in the analyses (i.e. baseline and at least one post-baseline assessment) varied for the symptom scores between 15-70 for topotecan and 12-65 for CAV. The study also reported significant differences in the length of time to worsening of dyspnea (p=0.046) and anorexia (p=0.003), with symptoms progressing more slowly in the topotecan group. However, data were not presented for any symptom for this latter outcome. It should also be noted that the symptom-specific questionnaire used in this study was not a validated instrument, and it is therefore unclear how reliable the results are.

Table 12 Symptoms (IV topotecan versus CAV)

Study	**Treatment arms**		**p-value**
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)	CAV (n=104)	
Improvement in disease-related symptoms, n/N* (%):			
Dyspnea	19/68 (27.9)	4/61 (6.6)	0.002**
Cough	17/69 (24.6)	9/61 (14.8)	0.160
Chest pain	11/44 (25.0)	7/41 (17.1)	0.371
Haemoptysis	4/15 (26.7)	4/12 (33.3)	0.706
Anorexia	18/56 (32.1)	9/57 (15.8)	0.042**
Insomnia	19/57 (33.3)	10/53 (18.9)	0.085
Hoarseness	13/40 (32.5)	5/38 (13.2)	0.043**
Fatigue	16/70 (22.9)	6/65 (9.2)	0.032**
Interference with daily activity	18/67 (26.9)	7/63 (11.1)	0.023**

*number of patients with baseline and at least one post-baseline assessment; ** $p < 0.05$.

Toxicity and Adverse events

Adverse events of all grades which were related, or possibly-related, to treatment and which occurred in more than 10% of participants were reported for the two treatment groups, and can be seen in Table 13 (see Appendix 6 for rates of adverse events of grades 1/2 and 3/4). The most frequently reported adverse events were nausea, fatigue, vomiting, anorexia and alopecia. Overall the groups appeared comparable for all reported adverse events, although in participants receiving topotecan the incidence of fatigue was lower and the incidence of alopecia was higher compared to those receiving CAV. The trial did not report a statistical comparison between treatment groups. Six deaths (5.6%) in the topotecan group and four deaths (3.8%) in the CAV group were related or possibly related to treatment. Of the 10 deaths, seven (four topotecan, three CAV) were associated with therapy-induced myelosuppression with sepsis/infection.

Table 13 Adverse events (IV topotecan versus CAV)

Study	**Treatment arms**	
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)	CAV (n=104)
Adverse events occurring in >10% of patients, n (%)	All grades	All grades
Nausea	42 (39.3)	42 (40.4)
Alopecia*	38 (35.5)	23 (22.1)
Fatigue	28 (26.2)	35 (33.7)
Vomiting	26 (24.3)	25 (24.0)
Anorexia	20 (18.7)	23 (22.1)
Stomatitis	15 (14.0)	13 (12.5)
Diarrhoea	13 (12.1)	13 (12.5)
Fever**	13 (12.1)	-
Constipation	-	16 (15.4)
Asthenia	-	14 (13.5)
Deaths		
Treatment-related	4	3
Possibly related or related to therapy	2	1

*reflects the number of patients who developed alopecia on study, approx. 30% in each arm presented to study with alopecia secondary to prior chemotherapy; **excludes febrile neutropenia.

The incidence of haematological toxicities are presented in Table 14. Grade 4 neutropenia occurred significantly more frequently in the topotecan group compared to CAV ($p<0.001$) for treatment courses (see Appendix 6), but this was not statistically significant for the participant analysis. In addition, the incidence of grade 4 thrombocytopenia ($p<0.001$) and grade 3/4 anaemia ($p<0.001$) was significantly higher in participants receiving topotecan. Infectious complications were reported to be similar between treatment groups.

Table 14 Toxicities (IV topotecan versus CAV)

Study	**Treatment arms**			
von Pawel *et al.*, 1999[59]	IV topotecan (n=107)		CAV (n=104)	
Haematologic toxicities, n/N* (%)	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	57/104 (54.8)	33/104 (31.7)	38/101 (37.6)	44/101 (43.6)
Neutropenia	19/104 (18.3)	73/104 (70.2)	15/99 (15.2)	71/99 (71.7)
Thrombocytopenia	30/104 (28.8)	30/104 (28.8)†	10/101 (9.9)	5/101 (5.0)†
Anaemia	41/104 (39.4)‡	3/104 (2.9)‡	18/101 (17.8)‡	2/101 (2.0)‡

*Represents the total number of patients with laboratory data available; $^{\dagger}p<0.001$; $^{\ddagger}p<0.001$ only when data for grade 3 and 4 was combined.

Summary of effectiveness of IV topotecan versus CAV

In the one RCT identified, topotecan and CAV were not found to be statistically significantly different for the primary outcomes of response and duration of response. Furthermore, there were no significant differences between groups for overall survival nor time to disease progression. QoL was not reported. Greater symptomatic improvement was seen in participants who received topotecan for four

symptoms as well as interference with daily activity, and symptoms progressed significantly more slowly in the topotecan group for two of eight symptoms evaluated. However the symptom-specific questionnaire used in this study was not a validated instrument. Overall the treatment groups were comparable for rates of adverse events, although the incidence of some haematological toxicities occurred significantly more frequently in the topotecan group compared to CAV. The trial was judged to be of reasonable methodological quality.

3.1.3.3 Oral topotecan versus IV topotecan

Survival

Two RCTs[56,58] compared oral and IV topotecan. In both trials, no statistically significant differences in overall survival were found between treatment groups (Table 15). Eckardt and colleagues[56] reported a median survival of 33.0 weeks (range 0.3 - 185.3) for oral participants and 35.0 weeks (range 0.7 - 205.3) for IV participants (hazard ratio 0.98, 95% CI 0.77, 1.25). At the time of analysis, 13.7% and 10.6% of oral and IV topotecan participants respectively were censored for survival. The one and two year survival rates appeared comparable between treatment arms (see Table 15), but a statistical test was not reported. Data collected during post-study monitoring showed that similar proportions of participants in each group had received third-line chemotherapy (33% and 35% in oral and IV groups respectively). It is not clear whether this may have had an impact on the overall survival rates presented.

In the study by von Pawel and colleagues (2001),[58] median survival was higher in the oral topotecan group (32.3 weeks, range 0.4 - 69.1) compared to the IV topotecan group (25.1 weeks, range 0.6 - 65.1), but this difference was not statistically significant (risk ratio [oral:IV] 0.84, 95% CI 0.53, 1.32). The study reports that regression modelling identified no baseline liver metastases (p=0.001) and lower PS (p=0.025) as statistically significantly associated with longer survival. The study only presents the p-values for these two significant factors, no data were presented, neither was there any discussion of the results of the other possible factors tested. This hinders any meaningful interpretation of the results of the modelling and caution is recommended. After accounting simultaneously for all prognostic factors, the risk ratio (oral:IV) of survival was reported to be 0.90 (95% CI 0.55, 1.47).

Table 15 Overall survival (oral topotecan versus IV topotecan)

Study	**Treatment arms**		**p-value, 95% CI**
Eckardt *et al.*, 2007[56]	Oral topotecan (n=153)	IV topotecan (n=151)	
Overall survival (weeks) median (range) 95% CI	33.0 (0.3 to 185.3)* 29.1 to 42.4	35.0 (0.7 to 205.3)* 31.0 to 37.4	Hazard ratio = 0.98 95% CI 0.77, 1.25 p=ns

Survival rate: at year 1 at year 2	 33% 12%	 29% 7%	Not reported
von Pawel *et al.*, 2001[58]	Oral topotecan (n=52)	IV topotecan (n=54)	
Overall survival (weeks) median (range)	32.3 (0.4 to 69.1)*	25.1 (0.6 to 65.1)*	Risk Ratio 0.84 95% CI 0.53, 1.32

*includes censored events

Response

Response rate was the primary outcome in both the Eckardt and colleagues study[56] and the von Pawel and colleagues[58] study and can be seen in Table 16. The difference in the overall response rate between those participants treated with oral topotecan and those treated with IV topotecan was reported to be -3.6% (95% CI -12.6%, 5.5%) in the Eckardt and colleagues[56] study. In contrast, von Pawel and colleagues[58] reported a difference in overall response rate of 8.3% (95% CI -6.6%, 23.1%). Although the overall responses in the two included studies were in different directions, neither was found to be statistically significantly different. The definition of response was not reported in the Eckardt and colleagues[56] trial. However, two participants in the oral topotecan group were reported to have a complete response, with the remaining 26 having a partial response. In the IV treatment group, all of those responding were classified as a partial response. Response in the von Pawel and colleagues[58] study was classified according to the WHO criteria. Of the responders in this study,[58] one participant in the oral topotecan group and two in the IV topotecan group were classified as complete responders, the remainder were partial responders.

Median time to response was the same (6.1 weeks) for both treatment arms of the Eckardt and colleagues[56] study. In the von Pawel and colleagues[58] study, there was a median of 18 weeks response in the orally treated participants compared to 14 weeks in the IV treated participants. This was not tested for statistical significance in the trial. In those responding in the Eckardt and colleagues[56] study, the duration of response was longer in the IV topotecan arm (median 25.4 weeks) compared to the oral topotecan arm (median 18.3 weeks), but no test of statistical significance was undertaken. In the von Pawel and colleagues[58] study, it is reported that regression modelling of response identified two factors that were statistically associated with increased probability of response – female gender (p=0.021) and no previous radiotherapy (p=0.015). The study only presented the p-values for these two significant factors, no data were reported. There was also no further discussion of the results of other possible factors, nor any data, so caution is required in interpreting these results of prognostic factors. Accounting simultaneously for all prognostic factors identified in the logistic regression analysis, oral topotecan participants were seen to be 1.6 (OR) times more likely to respond than IV topotecan participants (95% CI: 0.50, 5.15).

Of those classified as non-responders in the Eckardt and colleagues[56] study, 17.6% of the oral topotecan treated participants and 23.2% of the IV topotecan treated participants were classified as having stable disease. Progressive disease was reported in 51.0% and 43.0% of participants in the oral topotecan group and IV topotecan groups respectively. The study reported that 38 participants were not assessable for response due to death, withdrawal or completion of treatment after one or two courses (although the study also reports this figure as 32, it is assumed this is an error). Of those classified as non-responders in the von Pawel and colleagues[58] study, 19.2% and 29.6% of participants in the oral and IV topotecan groups respectively were classified as stable disease. Progressive disease was seen in 30.8% of those treated with oral topotecan compared to 42.6% of those treated with IV topotecan. Finally, in this study,[58] 26.9% and 13.0% of participants in the oral and IV topotecan groups respectively were classified as not assessable. No definitions for these classifications were reported in either study, and no statistical analyses of any differences between groups were undertaken.

Table 16 Response (oral topotecan versus IV topotecan)

Study	**Treatment arms**		**p-value, 95% CI**
Eckardt *et al.*, 2007[56]	Oral topotecan (n=153)	IV topotecan (n=151)	
Overall response rate**,** n (%) -complete response -partial response	28 (18.3%) 95% CI 12.2% to 24.4% 2 (1.3%) 26 (17.0%)	33 (21.9%) 95% CI 15.3% to 28.5% 0 33 (21.9%)	Difference (oral – IV) -3.6% 95% CI -12.6% to 5.5%
Time to response (weeks), median (range)	n=28 6.1 (4.4 to 17.7)	n=33 6.1 (2.1 to 13.9)	Not reported
Response duration (weeks) median (range)	n=28 18.3 (9.0 to 65.4)	n=33 25.4 (8.4 to 132.1)*	Not reported
Non-responders, n (%)* -stable disease -progressive disease -not assessable	 27 (17.6%) 78 (51.0%) 20 (13.1%)	 35 (23.2%) 65 (43.0%) 18 (11.9%)	Not reported
von Pawel *et al.*, 2001[58]	Oral topotecan (n=52)	IV topotecan (n=54)	
Overall response rate, n (%) -complete response -partial response	12 (23.1) 95% CI 11.6, 34.5 1 (1.9) 11 (21.2)	8 (14.8) 95% CI 5.3, 24.3 2 (3.7) 6 (11.1)	Difference 8.3% 95% CI -6.6% to 23.1%
Response duration (weeks), median	n=12 18	n=8 14	Not reported
Non-responders, n (%) -stable disease -progressive disease -not assessable	 10 (19.2) 16 (30.8) 14 (26.9)	 16 (29.6) 23 (42.6) 7 (13.0)	Not reported

* n=38 were classed as not assessable (although states n= 32 in the text)

Time to disease progression

The median time to disease progression in the Eckardt and colleagues[56] study was reported to be 11.9 weeks in the oral topotecan group and 14.6 weeks in the IV topotecan group. The trial publication does not report any statistical analyses of these data between the two groups, but it would appear that IV topotecan led to a longer duration before the disease progressed than oral topotecan. Conversely, in the von Pawel and colleagues[58] study the median time to disease progression was reported to be 15 weeks in the oral topotecan group and 13 weeks in the IV topotecan. The risk ratio was 0.90 (95% CI 0.59, 1.39) suggesting no differences between the two treatment options. von Pawel and colleagues[58] report that regression modelling of time to progression identified female gender (p=0.041), no liver metastases at baseline (p=0.020) and lower PS (p=0.036) as associated with longer time to progression. No data were presented for these or any other factors tested in the model and therefore caution is recommended when interpreting these results.

Table 17 Time to disease progression (oral topotecan versus IV topotecan)

Study	**Treatment arms**		**p-value, 95% CI**
Eckardt *et al.*, 2007[56]	Oral topotecan (n=153)	IV topotecan (n=151)	
Time to progression (weeks), median (range)	11.9 (0.3 to 149.0)* 95% CI 9.7, 14.1	14.6 (0.7 to 177.9)* 95% CI 13.3, 18.9	Not reported
von Pawel *et al.*, 2001[58]	Oral topotecan (n=52)	IV topotecan (n=54)	
Time to progression (weeks), median (range)	15 (0.4 – 69.1)	13 (0.6 – 65.1)*	Risk ratio 0.90 (95% CI 0.59, 1.39)

*includes censored events

Quality of life

In the Eckardt and colleagues[56] trial health related QoL (HRQoL) was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. This is a 44-item self-reported instrument, which is reported to be a validated scale and includes four generic dimensions and a sub-scale specific to lung cancer. In addition, the Trial Outcome Index (TOI) was also derived from a sub-group of data. Very little data were presented in the study report, but the authors state that the mean change from baseline indicated no statistical difference between treatment groups for sub-scale dimension scores or the lung cancer scale (LCS), the TOI or the FACT-L total scores. The mean change from baseline to the last course of treatment also showed no statistical differences between groups (no data provided). QoL was not assessed in the von Pawel and colleagues[58] study.

Symptoms

In those reporting symptoms at baseline, von Pawel and colleagues[58] reported the proportion showing an improvement, classed as sustained improvement needed until the next treatment cycle. Symptoms were evaluated on a 4-point scale (1 = not at all, 2 = a little bit, 3 = quite a bit, 4 = very much) and

although based on the Lung Cancer Symptom Score, it was reported that this was not a validated scale. The proportions of participants with improved symptoms were generally between 13-42% across all symptoms. The scores were not tested for statistically significant differences between the two groups (see Appendix 6 for full results). In the oral and IV topotecan groups respectively, the symptoms with the greatest reduction were chest pain (42.1% vs 31.8%), haemoptysis (33.3% vs 40%) and hoarseness (35.7% vs 37.5%). Symptoms scores were not reported by Eckardt and colleagues.[56]

Adverse events and toxicity

Eckardt and colleagues[56] and von Pawel and colleagues[58] report the rates of non-haematological adverse events (see Table 18). Rates of grade 3 and 4 adverse events generally appeared to be similar across the different routes of administration of treatment in the Eckardt and colleagues[56] study, with the exception of grade 3 diarrhoea and anorexia which were more frequently observed in the oral topotecan group. In the von Pawel and colleagues[58] study, rates of non-haematological adverse events were also seen to be similar between the two treatment regimens, with perhaps the exception of vomiting, pneumonia, and diarrhoea which appeared to occur more frequently in the oral topotecan group, and alopecia which occurred more frequently in the IV topotecan group. However, no statistical analyses of these rates were reported. In the Eckardt and colleagues[56] study there were six deaths in the oral topotecan group and four in the IV topotecan group. The study reports that participants died either as a result of hematologic toxicity, septic shock related to topotecan treatment or of other causes possibly related to topotecan treatment. In the von Pawel and colleagues[58] study, two participants (1.9%) in the oral topotecan group died of sepsis and febrile agranulocytosis.

Table 18 Adverse events (oral topotecan versus IV topotecan)

Study	**Treatment arms**					
Eckardt *et al.*,2007[56]	Oral topotecan (n=153)			IV topotecan (n=151)		
Non-haematologic Adverse effects, n(%)	Grade 3	Grade 4		Grade 3	Grade 4	
Diarrhoea	11 (7.2)	1 (0.7)		3 (2.0)	1 (0.7)	
Fatigue	10 (6.5)	0		10 (6.6)	2 (1.3)	
Dyspnea	9 (5.9)	3 (2.0)		10 (6.6)	5 (3.3)	
Anorexia	8 (5.2)	0		3 (2.0)	1 (0.7)	
Nausea	6 (3.9)	0		3 (2.0)	1 (0.7)	
Asthenia	4 (2.6)	3 (2.0)		7 (4.6)	3 (2.0)	
Fever	3 (2.0)	3 (2.0)		4 (2.6)	6 (4.0)	
von Pawel *et al.*,2001[58]	Oral topotecan (n=52)			IV topotecan (n=54)		
Adverse effects, n (%)*	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Vomiting	6 (11.5)	0	0	2 (3.7)	0	0
Dyspnoea	5 (9.6)	0	0	5 (9.3)	0	1 (1.9)
Fever	2 (3.8)	1 (1.9)	1 (1.9)	1 (1.9)	0	0
Pneumonia	3 (5.8)	1 (1.9)	0	0	0	1 (1.9)
Diarrhoea	4 (7.7)	0	0	0	0	0

Pulmonary embolism	1 (1.9)	0	2 (3.8)	0	0	1 (1.9)
Asthenia	3 (5.8)	0	0	5 (9.3)	0	0
Fatigue	3 (5.8)	0	0	1 (1.9)	0	0
Alopecia	1 (1.9)	0	0	7 (13.0)	0	0
Abscess	0	0	0	2 (3.7)	1 (1.9)	0

*occurring in ≥ 5% participants

Associated toxicities (grade 3 and 4) from the respective treatments were also reported in the studies by Eckardt and colleagues[56] and von Pawel and colleagues,[58] and can be seen in Table 19. Based on observation of this data it would appear that rates are similar across the treatment groups in the Eckardt and colleagues[56] study. Grade 4 neutropenia and grade 3 anaemia appeared to occur more frequently in the IV treated participants than the oral treated participants, while grade 4 thrombocytopenia appeared to occur more frequently in the oral treated participants. In the Eckardt and colleagues[56] study the authors also report that fever and/or infection (≥ grade 2) associated with grade 4 neutropenia, together with sepsis, occurred in 5% of courses in both groups. In the von Pawel and colleagues[58] study, rates of toxicities were also observed to be similar between the two treatment arms, with the exception of grade 4 neutropenia which was reported to be statistically significantly more frequently observed in the IV topotecan treatment group (p=0.001). The trial also reports that the median duration of grade 4 neutropenia was similar between groups (oral group 7 days, IV group 6 days). Although the trial does not report a statistically significant difference between rates of grade 3 leukopenia, it can be observed that the rates are higher in the IV topotecan group compared to the oral topotecan group.

Table 19 Toxicities (oral topotecan versus IV topotecan)

Study	**Treatment arms**			
Eckardt *et al.*,2007[56]	Oral topotecan (n=153)		IV topotecan (n=151)	
Toxicities, n (%)*	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	64 (42.7)	34 (22.7)	74 (49.3)	39 (26.0)
Neutropenia	39 (26.2)	70 (47.0)	35 (23.6)	95 (64.2)
Thrombocytopenia	30 (20.0)	43 (28.7)	38 (25.3)	27 (18.0)
Anaemia	26 (17.3)	8 (5.3)	42 (28.0)	4 (2.7)
von Pawel *et al.*,2001[58]	Oral topotecan (n=52)		IV topotecan (n=54)	
Toxicities, %	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	21.6	35.3	26.9	67.3
Leukopenia	27.5	17.6	45.3	28.3
Thrombocytopenia	25.5	27.5	24.5	24.5
Anaemia	27.5	3.9	26.4	3.8

*occurring with a frequency of ≥10% in either treatment group

Summary of effectiveness of IV topotecan versus oral topotecan

There were no statistically significant differences in overall survival between treatment groups for either of these studies. Similarly, no statistically significant differences were seen in the overall

response rate. IV topotecan appeared to lead to a longer duration before disease progression than oral topotecan in one study,[56] but this was not supported by the other.[58] QoL was assessed in one of the included studies[56] and there appeared to be no statistically significant differences between treatment groups. No statistical analyses of adverse event rates were reported in either study. Associated grade 3 and 4 toxicities were similar between IV topotecan and oral topotecan in the studies with the exception of grade 3 or 4 neutropenia which appeared to occur more frequently in the IV treated participants. While these studies suggest that IV and oral topotecan are equivalent, it should be noted that neither study was powered to test for equivalence or non-inferiority. In addition, these studies were of unknown methodological quality due to the lack of details reported. Furthermore, it should be considered that there is some uncertainty over whether the Eckardt and colleagues[56] study fully meets the inclusion criteria of the current review. For these reasons, it was deemed inappropriate to combine the two trials in a meta-analysis.

3.1.3.4 IV amrubicin versus IV topotecan

Survival

One RCT (Inoue and colleagues[63]) was included which compared IV topotecan with IV amrubicin. In this trial, median overall survival was not statistically significantly different (p=0.17) between the amrubicin treated participants (8.1 months) and the topotecan treated participants (8.4 months). Progression free survival between the treatment groups was also not statistically significant (p=0.16), with a median 3.5 months for the amrubicin group versus 2.2 months for the topotecan group (see Table 20). One participant in the amrubicin arm received no treatment due to rapid disease progression, and hence was not included in the analysis. The paper reported a sub-group analysis of overall survival and progression free survival according to relapse type. No statistical tests of the difference between treatment groups were presented (see Appendix 6), although for both outcomes the trend was for participants with sensitive disease to do better than those with refractory disease. However, it is unclear if the study was powered for this analysis. Many of the participants received subsequent (third-line or later) chemotherapy after disease progression (48% and 70% in the amrubicin and topotecan groups respectively) with cross-over administration performed in 41% of participants (17% and 63% respectively). In addition, the dose of topotecan used (1.0 mg/m^2) was lower than the UK recommended dose (1.5 mg/m^2). It is not clear whether these factors may have had an impact on the overall survival rates shown.

Table 20 Overall survival (IV amrubicin versus IV topotecan)

Study	**Treatment arms**		**p-value**
Inoue *et al.*, 2008[63]	IV amrubicin (n=29)	IV topotecan (n=30)	
Overall survival, median (months)	8.1	8.4	*p*=0.17
Progression-free survival, median (months)	3.5	2.2	*p*=0.16

Response

Response rate was the primary outcome in this study and was assessed according to the RECIST criteria. There was a statistically significant difference in the overall response rate of 38% (95% CI 21, 58) for participants who received amrubicin compared to 13% (95% CI 1, 25) for participants who received topotecan (*p*=0.039). Again, it should be noted that a lower dose of topotecan was used. In addition, there were some discrepancies in the reporting of confidence intervals between the full paper, abstract and conference presentation (see Appendix 6). The study reported details of participants with complete or partial response, as well as stable or progressive disease in each treatment arm. No participants in either group showed a complete response. It can be seen in Table 21 that a greater proportion of participants receiving amrubicin achieved a partial response (38% vs 13% topotecan), whilst a greater proportion of participants receiving topotecan were rated as having progressive disease (53% vs 21% amrubicin). Stable disease was achieved in 41% and 33% of the amrubicin and topotecan groups respectively. However, no statistical analysis for this data were reported.

Inoue and colleagues[63] performed sub-group analyses examining the effects of sensitive and refractory relapse, and performance status 0 -1 versus 2 on overall response rates between treatment groups. No statistically significant differences were shown (all p>0.05, see Appendix 6), but it should be noted that it is unclear if the study was powered for these analyses. In addition, the trial also reports further analysis of three prognostic factors (age, gender and prior chemotherapy regimen) but no data were presented.

Table 21 Response (IV amrubicin versus IV topotecan)

Study	**Treatment arms**		**p-value**
Inoue *et al.*, 2008[63]	IV amrubicin (n=29)	IV topotecan (n=30)	
Overall response, n (%); 95% CI	11 (38) 21-58*	4 (13) 1-25†	*p* =0.039
Responses, n (%): - complete response - partial response - stable disease - progressive disease	 0 (0) 11 (38) 12 (41) 6 (21)	 0 (0) 4 (13) 10 (33) 16 (53)	

*20-56 in abstract; †4-31 in conference presentation.

The study also reported disease control rates, but no definition was supplied and these are therefore not reported here.

Time to disease progression

Time to disease progression was not reported by this study.

Quality of life

QoL was not reported by this study.

Adverse events and toxicity

Adverse events can be seen in Table 22. Unlike the other included studies, febrile neutropenia was presented as a non-haematological toxicity in this study. Although rates were not tested for statistical significance, it can be observed that participants in the amrubicin treatment arm suffered much higher rates of adverse events of grade three or four, with the exception of diarrhoea which was more frequently observed in the topotecan group. It is not clear whether the lower dose of topotecan used in this trial affected the rates of adverse events shown.

Table 22 Adverse events (IV amrubicin versus IV topotecan)

Study	**Treatment arms**							
Inoue *et al.*, 2008[63]	IV amrubicin (n=29)				IV topotecan (n=30)			
Non-haematological toxicity, n	Grade			≥ Grade 3	Grade			≥ Grade 3
	2	3	4	%	2	3	4	%
Fatigue	4	5	0	17	3	2	0	7
Febrile neutropenia	-	4	0	14	-	1	0	3
Infection	0	2	1	10	0	1	0	3
Anorexia	4	2	0	7	4	0	0	0
Nausea/vomiting	1	1	0	3	1	0	0	0
Stomatitis	1	1	0	3	0	0	0	0
Diarrhoea	0	0	0	0	0	1	0	3
Fever	2	0	0	0	1	0	0	0
Constipation	2	0	0	0	0	0	0	0
Pneumonitis	1	0	0	0	2	0	0	0

Grades of haematological toxicity were also reported in the study by Inoue and colleagues[63] and can be seen in Table 23. No statistical analyses of grades or treatment arms were reported. Based on observation, it would appear that participants in the topotecan treatment arm suffered higher rates of associated toxicity of grades three or four for anaemia and thrombocytopenia, and lower rates of neutropenia than the amrubicin group. There was a discrepancy between the abstract[62] and full publication[63] in the reporting of neutropenia, with the abstract[62] reporting a higher rate (97%) in the amrubicin arm. One patient in the amrubicin treatment arm is reported to have died of neutropenic sepsis developing from urinary tract infection; no other deaths are reported in the study.[63]

Table 23 Toxicities (IV amrubicin versus IV topotecan)

Study	**Treatment arms**							
Inoue *et al.*, 2008[63]	IV amrubicin (n=29)				IV topotecan (n=30)			
	Grade			≥ Grade 3	Grade			≥ Grade 3
Haematological toxicity, n	2	3	4	%	2	3	4	%
Neutropenia	0	5	23	93*	3	13	13	87
Thrombocytopenia	6	7	1	28	5	9	3	40
Anaemia	15	3	3	21	12	6	3	30

*97 in abstract[62]

Summary of effectiveness of IV amrubicin versus IV topotecan

In this study comparing amrubicin with topotecan, the primary outcome of overall response rate was shown to be in favour of the amrubicin treatment arm. Overall survival and progression free survival were not significantly different between the two groups. Time to disease progression and QoL were not reported. Based on observation, rates of adverse events generally appeared to be higher for patients in the amrubicin treatment arm. Rates of toxicity varied, however neutropenia was higher in the amrubicin group. It should be noted that the topotecan dose of 1.0 mg/m^2/day (the approved dose in Japan) was below the UK recommended dose of 1.5 mg/m^2/day. In addition, the study is of an unknown quality due to the lack of details reported in the trial.

3.1.4 Ongoing studies

The following studies were identified in searches and are currently ongoing:

Wang XS, Hou M, Xue SL, Wu TX. Topotecan for small cell lung cancer. (Protocol) *Cochrane Database of Systematic Reviews* 2008, Issue 2 (date of most recent substantive amendment - 26 January 2008). This systematic review aims to investigate the role of topotecan in the management of patients with SCLC by considering its clinical effectiveness and safety. (The review will include participants who were previously untreated, will consider topotecan in combination with any other chemotherapy agent, and will also consider topotecan used in first-line treatment).

NCT 00319969. A phase II, randomised trial comparing IV amrubicin (40 mg/m^2) versus IV topotecan (1.5 mg/m^2) in adults with extensive-stage SCLC sensitive to first-line (platinum-based) chemotherapy. Study type: open-label, multi-centre, phase II, parallel RCT. Sample size: 76. Start date: April 2006. Estimated end date: January 2009 (final data collection date for primary outcome measure). Status: the study is ongoing, but not recruiting participants. Funding: Calgene Corporation. Funding amount: not reported.

NCT 00547651. A phase III, randomised trial comparing IV amrubicin (40 mg/m^2) versus IV topotecan (1.5 mg/m^2) in adults with extensive-stage or limited-stage SCLC who are sensitive or refractory to first-line (platinum-based) chemotherapy. Study type: open-label, multi-centre, phase III, parallel, safety/efficacy RCT. Estimated sample size: 620. Start date: September 2007. Estimated end date: March 2011 (final data collection date for primary outcome measure). Status: the study is currently recruiting participants. Funding: Calgene Corporation. Funding amount: not reported.

4 ECONOMIC ANALYSIS

4.1 Methods for economic analysis

The aim of this section is to assess the cost effectiveness of topotecan compared to existing regimens in second-line chemotherapy for SCLC. The economic analysis comprises of:

- a systematic review of the literature on the cost effectiveness of topotecan and a review of the QoL of people suffering with SCLC. An additional search was undertaken to inform different approaches to modelling disease progression.
- a review of the MS to NICE.
- a presentation of the SHTAC independent economic model and cost effectiveness evaluation.

4.1.1 Systematic review of the existing cost-effectiveness

A systematic literature search was undertaken to identify economic evaluations of topotecan compared to other regimens as a second line chemotherapy in SCLC. The details of the search strategy are documented in Appendix 3. The MS was reviewed for any additional studies that were missed by the searches.

Results of the systematic review

A total of 49 potentially relevant publications of economic evaluations relating to topotecan in SCLC were identified in the search. No relevant cost-effectiveness analyses were identified after screening of the titles and abstracts.

4.1.2 Review of research on quality of life

The details of the search strategy for QoL are in Appendix 3. A total of 122 publications relating to topotecan in SCLC were identified.

The search identified one potentially relevant study that could be used to populate the model with the relevant outcome measures as specified in the scope. This was the RCT by O'Brien and colleagues,[57]

which used the EQ-5D to assess HRQoL in trial participants. A further search of recent abstracts was undertaken, which identified one additional QoL abstract based on the O'Brien and colleagues RCT by Chen and colleagues.[64] Both the trial report, by O'Brien and colleagues[57] and the abstract by Chen and colleagues[64] have been data extracted and critically appraised in the clinical effectiveness section (see section 3.1.3.1).

4.1.3 Review of manufacturer's submission

The MS consisted of a written report and electronic model supporting the cost-effectiveness analyses.

A brief overview of the manufacturer's cost-effectiveness analysis, including the approach taken to model disease progression and the effects of treatment, followed by a critical appraisal of the cost effectiveness analysis, is presented here.

GSK submission to NICE;[51] Cost effectiveness analysis

Overview

The stated aim of the analysis was to assess the cost effectiveness of oral topotecan plus BSC against BSC alone in people with relapsed SCLC in whom treatment with IV chemotherapy is not considered appropriate. The cost effectiveness analysis was based on participant level data from the O'Brien and colleagues RCT.[57] BSC in the evaluation consisted of analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, red blood cell (RBC) transfusions, deep relaxation therapy, and palliative radiotherapy or surgical procedures. Participants with the active treatment were also eligible for BSC alongside treatment with oral topotecan.

The base case analysis is reported for the whole cohort of participants who received oral topotecan plus BSC compared to BSC alone after relapse of SCLC from the O'Brien and colleagues RCT.[57] Several subgroup analyses were also reported in the MS including different times to progression, sex, performance status and liver metastases. The maximum survival in the trial was 1,480 days, or 71 21-day survival periods.

The perspective of the economic analysis is stated as being that of the NHS and PSS, capturing only those costs and benefits that are directly relevant to the intervention. The submission reports lifetime costs and outcomes (life years gained and QALYs) for each treatment arm. An incremental analysis of costs and outcomes of topotecan plus BSC compared to BSC alone was undertaken.

Model of cost-effectiveness of topotecan

The MS reports that a systematic review of economic evaluations for oral topotecan in SCLC was undertaken. The search of databases was limited to the NHS EED and PubMed databases. The search identified nine cost effectiveness studies, with eight being for topotecan in ovarian cancer and a further study in mobilising peripheral blood stem cells - there were no studies identified for topotecan in SCLC. This is consistent with the SHTAC systematic literature search (see section 4.1.1).

The approach taken in the MS model is outlined below and an outline review based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[66] the requirements of NICE for the submission on cost-effectiveness (reference case)[67] and suggested guideline for good practice in decision modelling by Philips and colleagues[68] given.

Modelling Approach

The model developed by the manufacturer was a trial based model. The multi-centre trial contained 141 participants with participant characteristics being evenly distributed between the two groups.[57] Median survival times were 13.9 weeks (95% CI, 11.1, 18.6) in the BSC alone group and 25.9 weeks (95% CI, 18.3–31.6) in the oral topotecan plus BSC group. The economic model used the data from the trial up until the final assessment period, when six participants (three in the BSC group and three in the topotecan plus BSC group) were still alive. The model assumed that all surviving participants died the day after this final assessment. The participant level survival data was divided into 21-day periods to reflect the study cycles in the RCT.

Health state utilities were collected using the EQ-5D during the RCT. This was done at the beginning of each cycle and up to and including cycle 12 for all participants in the topotecan plus BSC group and the BSC group. The quality adjusted survival was calculated by multiplying individual survival in each 21 day period by the corresponding EQ-5D period score for that participant. There were a total of 1,548 21 day survival periods across the 141 participants in the RCT. Individual data was, however, only available for 600 periods.

The MS reports that the 948 missing EQ-5D values in the data were mainly due to progression of disease towards death. The MS used the observed mean EQ-5D scores for the first 12 cycles from both arms of the trial, to take account of the missing data from each of the corresponding cycles. A last observation carried forward approach (LOCF) was used for the topotecan plus BSC group before participants entered a progressive disease state and after treatment had finished and, also, in BSC alone group until five periods from death. For all other missing EQ-5D data, the MS used data from the BSC group's EQ-5D scores for the five 21-day cycles of disease progression before death by

applying this backwards from the period in which the participant died. This was done for both BSC and topotecan groups. If the participant survived more than the five periods in the progressive disease state, the figures for the fourth period before death were applied backwards until the start of progressive disease.

Two categories of adverse events were recorded in the trial and used in the model; haematological adverse events and non-haematological adverse events. The incidence of non-haematological adverse events was reported as a percentage for each grade. Haematological events were reported on the basis of their resource use alone in terms of transfusions and granulocyte colony stimulating factor (GCSF) and antibiotics. No explicit reduction in QoL was recorded for experiencing an adverse event due to the ongoing recording of EQ-5D valuation throughout the trial.

The costs applied in the MS were split into five main categories: drug cost of oral topotecan, oral topotecan drug administration costs, drug monitoring costs, cost of non-disease progression in the oral topotecan group and adverse events associated with oral topotecan. Not all resource use was collected in the trial and therefore clinical opinion was used to fill in gaps in the resource use.

Oral topotecan used in the trial was administered in 0.25 mg or 1.00 mg capsules and was dosed at 2.3mg/m^2/day on days 1 to 5 of 21 day cycles for up to 12 cycles.[57] The drug cost was calculated by multiplying the total drug use of topotecan per participant by the drug acquisition costs. The average cost of oral topotecan in the MS was calculated at £2500. The MS assumed that oral topotecan was delivered on an outpatient basis on days 1 to 5 and this was verified by clinical opinion. An additional small dispensing fee was also included. The total average cost for drug administration of all topotecan in the trial was £713. Drug monitoring costs for pathology monitoring, haematological toxicity monitoring and biochemical monitoring was taken from a study that included oral topotecan used as a chemotherapy in ovarian cancer which had an average cost of £39.[69]

The cost of progression to death was assumed to be the same for both groups and was not included in the incremental analysis. The cost of non disease progression for the topotecan and BSC group was based on clinical feedback and included outpatient visits, GP visits, chest X-rays, and blood tests every four weeks. The total costs of non disease progression were £758.

Non haematological adverse events were reported in terms of a percentage for grades 1 to 4 for diarrhoea, fatigue, nausea and vomiting. Corresponding resource use was then applied to the occurrence of these events. However, haematological adverse events were accounted for in terms of transfusions, GCSF and antibiotics that were used in the trial. The average costs of treating adverse events resulting from oral topotecan in the MS were £1660.

The MS assumed that any PSS costs for additional care given outside a hospital were equally likely to occur in both the BSC alone and topotecan plus BSC groups. Unit costs from different base years (from 2003 to 2007) were included in the model. The cost year for the model is 2007/08. All costs reported in other years were inflated to 2007/8 costs using the NHS Hospital and Community Health Service (HCHS) Pay and Prices Index.[70] This only includes data up to the 2006/7 year. An assumption was made, therefore, that the percentage increase in the HCHS pay and prices from 2006/07 to 2007/08 would be the same as that from 2005/06 to 2006/07.

Model/cost effectiveness results

The MS only reports costs that were likely to be higher in the oral topotecan plus BSC arm of the trial. Outcomes were reported in terms of life years and QALYs. The oral topotecan plus BSC arm in the base case analysis resulted in 0.259 years of additional life and 0.211 QALYs over the BSC alone arm of the trial. The incremental cost of the oral topotecan and BSC arm was £5,671 compared to the BSC alone arm. The ICER per life year gained is £21,878 and per gained QALY is £26,833.

Drug costs were the largest single component of total costs (44%). The cost of treating adverse events was 29% of the total costs. The cost of non progressive disease was 13% and monitoring chemotherapy was 13% of total costs. Drug monitoring accounted for 1% of total costs.

The MS concludes that oral topotecan plus BSC versus BSC alone is likely to be a cost effective therapy in people with relapsed SCLC, who are not considered suitable for standard IV chemotherapy.

Outline appraisal of the manufacturer cost effectiveness analysis

A summary of the MS compared with the NICE reference case requirements are given in Table 24. See Appendix 8 for a tabulation of the critical appraisal of the submission against Drummond and colleagues' checklist.[66]

Table 24 Assessment of GSK submission against NICE reference case requirements

NICE reference case requirements	Included in submission
Decision problem: as per the scope developed by NICE	?[#]
Comparator: alternative therapies routinely used in the UK NHS	?[†]
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓[+]
Type of economic evaluation: cost-effectiveness analysis	✓
Synthesis of evidence on outcomes: based on a systematic review	No evidence synthesis
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: use of a	✓

standardised and validated generic instrument	
Method of preference elicitation for health state values: choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: representative sample of the public	✓
Discount rate: 3.5% p.a. for costs and health effects	✓

Notes (✓=yes; × = no; ? = uncertain; N/A=not applicable):
[#] scope states that oral and IV topotecan be compared with each other. Also states that CAV is a comparator. The economic evaluation includes only oral topotecan and BSC: CAV was excluded since topotecan (oral or IV) would not be a cost-effective alternative, therefore economic evaluation is limited to patients not considered suitable for CAV. IV topotecan was excluded on basis of similar efficacy, but higher acquisition and administration cost, therefore unlikely to be a cost effective alternative.
[†] if the reasoning for exclusion of CAV is accepted then comparator to topotecan is BSC, as in the economic evaluation.
[+] economic evaluation used utilities derived using EQ-5D administered to participants during treatment with oral topotecan plus BSC and with BSC alone. It is not clear how far the EQ-5D utilities include the effects of treatment-related toxicity for participants treated with oral topotecan.

Outline review of the modelling approach

Model structure/structural assumptions

The model used the participant level survival data for the oral topotecan with BSC arm and the BSC alone arm from the O'Brien and colleagues[57] trial to estimate survival benefit. The effect of oral topotecan was to increase life expectancy compared to BSC by extending time before the disease progresses. BSC is intended to reduce the impact of disease progression rather than affect disease progression itself.

The time horizon used in the economic evaluation is the length of the trial. No additional modelling was undertaken to extend survival beyond the end of the trial. The MS reported that there were six remaining participants (three in topotecan group and three in the BSC alone group) who were still alive at the end of the trial and it was assumed all died the day after the end of the study. However, from the Kaplan-Meier plot of overall survival from the O'Brien and colleagues[57] trial this does not appear to be the case. It appears that there are fewer survivors in the BSC arm than the three survivors reported in the MS. The reason for this discrepancy is unclear. Nevertheless, assuming that there are three survivors in each arm, based on the participant level data in the manufacturer's model, this represents just over 4% of the population in each arm. There is a possibility that this could have underestimated the survival benefit for either arm of the trial.

Adverse events were incorporated into the model through the incidence of grade 1 to 4 non-haematological events as they occurred in the trial. Haematological events were incorporated into the model using resource use of transfusions, the use of GCSF and antibiotics, rather than their incidence. The different methodology used to account for adverse events is thought not to have seriously impacted upon the results of the model. The large amount of missing EQ-5D data in the RCT means it

is unclear whether the expected disutility from having an adverse event will have been adequately picked up. Furthermore, it is not clear if the EQ-5D data collected at three week intervals captures the impact of the adverse events well.

An assumption was made that there would be a reduction in health utility once the disease progressed in the topotecan group. This was accounted for by using utility data from the BSC participants for the last five periods until death. This seems to be a fair assumption, as there is likely to be a reduction in utility once the disease progresses in the topotecan group that corresponds to the BSC group's health state valuations in the five periods preceding death.

Data inputs

Participant level data was taken from the O'Brien study[57] and this provided inputs on the survival length of participants in the trial, resource use and health utilities. Expert opinion was used to give additional information on resource use. The unit cost data was taken from national published sources.

Health utilities were recorded throughout the trial at the beginning of each cycle. However, many of the health state valuations were missing due to progression of the disease in participants. This causes great uncertainty in the model as only 39% of the survival periods were available. An average of observed cycle EQ-5D data matched to the corresponding cycle with missing data and the LOCF technique were used to overcome this missing data. More rigorous modelling methods, for example a regression analysis, could have been employed to take account of this missing data.

The average EQ-5D scores used for imputation are highly variable across cycles 1 to 12. The variability reflects the uncertainties that are involved with using this approach. Firstly, the pooled data on average EQ-5D were used from both arms of the trial. No justification of pooling both groups of participants was given, but it is likely to have been adopted due to the small number of observations that occurred as the number of cycles increased. This may have underestimated the health benefit in the topotecan arm in the first five cycles of the trial, as this was when the majority of BSC participants were experiencing disease progression towards death and appear to have reported lower mean EQ-5D scores per cycle at this time. Secondly, one would expect EQ-5D scores to decline as time goes on and people progress towards death. However, there is an upward trend in the mean EQ-5D scores up to cycle 7. This may reflect sicker participants dying first and leaving a higher proportion of healthier participants who will tend to report higher EQ-5D scores. This is likely to overestimate utility in the topotecan arm of the trial as these participants lived longer than the BSC participants. Finally, the lack of observations for the last five cycles also causes fluctuations in the average EQ-5D scores, with only one observation from the BSC group accounting for cycles 11 and 12. The impact on the model of

using this approach to take account of missing data is unclear, as it is likely to roughly underestimate the utility in the first half of the cycles and roughly overestimate utility in the last half of the cycles.

The MS used a LOCF approach in both groups, prior to disease progression and once the first 12 cycles were completed. This also only affects a very small number of participants in the trial and is unlikely to have a large effect on the model results.

The MS reported that only cost components that were higher in the topotecan arm were included in the model, suggesting that this would probably be most likely to over-estimate the incremental costs associated with oral topotecan compared to BSC and was therefore a conservative assumption.[51] This seems reasonable; however, it is likely that palliative care will be experienced at different time periods in both groups and discounting may underestimate incremental costs here in favour of topotecan.

Participant level data for resource use was reported for most of the categories of cost in the model. However, not all resource use was recorded. The manufacturer used expert opinion to estimate resource use that was not recorded in the trial, such as treatment of non-haematological events. We discussed these assumptions with clinical experts who concluded that they appeared to be reasonable.

Assessment of uncertainty

Uncertainty is addressed using both a deterministic and a bootstrap analysis. The deterministic sensitivity analysis addresses issues of methodological uncertainty (varying discount rates) and parameter uncertainty (different assumptions about utility weights, cost of additional non- progressive disease survival, cost of drug monitoring, cost of treating adverse events, cost of PSS events and assumptions about how the drug is administered). Only the ICER is reported in these analyses and so no comment can be made about the changes in total costs and outcomes. The ICERs were fairly insensitive to the changes made in the deterministic analysis with a range from £22,512 (for halving the cost of adverse events) to £40,253 (for oral topotecan being administered during a daily outpatient visit for five days each cycle). Other scenarios that raise the ICERs were doubling the cost of treating adverse events (£34,468), the cost of additional non-progressive disease survival being doubled (£30,421) and using the combined mean EQ-5D score at each cycle and LOCF approach to account for missing data (£33,816).

Sample uncertainty was addressed for the base case analysis using a bootstrap analysis. Non-paramatic bootstrap methods are used to create confidence intervals around a statistic of interest, which are derived from repeatedly drawing samples with replacement from the original treatment arms of the study.[71] In this analysis, the statistic of interest was the ICER for oral topotecan plus BSC and BSC alone. The

analysis used 10,000 bootstrap replications and presented the resulting 95% confidence ellipses for the ICERs. Oral topotecan and BSC in the bootstrap analysis was always associated with increased costs (incremental costs between £4,000 and £7,500) and usually with improved QALY outcomes (incremental QALYs between zero and approximately 0.6). The majority of the ICERs (98.31%) for oral topotecan and BSC (compared with BSC alone) were found in the upper right quadrant of the cost effectiveness plane (i.e. oral topotecan and BSC was more effective and more costly than BSC alone). The remaining 1.69% of replications are in the upper left quadrant, in which oral topotecan plus BSC is less effective and more costly than BSC alone. A cost effectiveness acceptability curve was presented. Oral topotecan and BSC had a probability of being cost effective relative to BSC of 22% at a willingness to pay threshold of £20,000 per QALY and 60% at a willingness to pay threshold of £30,000 per QALY.

A subgroup analysis was also presented for time to progression that was less than or equal to 60 days and over 60 days, performance status 0/1, sex and the presence of liver metastases. Oral topotecan plus BSC was more cost effective per QALY gained in patients for whom the time to progression from prior therapy was less than or equal to 60 days (£17,946) in females (£11,708) and those with no liver metastases (£21,291) and a performance status of 2 (£25,544). The sub groups where ICERs were higher than a willingness to pay threshold of £30,000 per QALY were in males (£74,175) and performance status of zero or 1 (£30,770), liver metastases (£56,534) and time to progression of over 60 days (£31,972).

A further analysis was undertaken in the time to progression of over 90 days and in the no liver metastases subgroups. It is important to note the small sample sizes for these data with only 30 and 51 participants respectively. No justification was given for more in depth analysis of these participant subgroups. However, these are the two subgroups that are most likely to benefit from oral topotecan after the less than or equal to 60 days time to progression group. The ICERs for the deterministic analysis, applying the same scenarios as used in the base case analysis, were in the range of £20,260 to £38,085 for the time to progression over 90 days and £17,804 to £32,043 for no liver metastases. The more conservative assumptions over the measurement of HRQoL, the drug administration costs and cost of treating adverse events, all produced ICERs over a willingness to pay threshold of £30,000 per QALY in the over 90 days to progression subgroup. The only scenario in the no liver metastases group, that was above the willingness to pay threshold of £30,000 per QALY, was the conservative assumption of drug administration cost being provided for five days of outpatient visits. A bootstrap analysis with 10,000 bootstrap replications was also undertaken in both subgroups. The bootstrap replications for both groups were predominantly in the upper right hand quadrant; 95.85% for the over 90 days to progression and 98.98% in the no liver metastases group. At a willingness to pay threshold of £20,000 per QALY oral topotecan plus BSC would be cost effective relative to BSC alone in the

over 90 days to progression and in the no liver metastases subgroups in 33% and 44% of cases respectively. If the threshold increased to £30,000, then these percentages would increase to 62% and 75% respectively.

Summary of general concerns

- It is unclear whether the disutility that would be expected from experiencing an adverse event in the topotecan group has been adequately represented due to the large amount of missing EQ-5D data and three week intervals between collections of EQ-5D data. This may be further biased due to healthier participants being more able and willing to fill in EQ-5D questionnaires than those who are experiencing an adverse event. If this is correct, then utility and therefore gain in QoL compared to BSC is likely to be an overestimation for the topotecan group.
- No modelling beyond the length of the trial was undertaken. A small but potentially significant number of participants were still alive at the end of the trial. However, it is not entirely clear how many participants in the trial were still alive, as the MS and Kaplan-Meier plot from the O'Brien and colleagues RCT[57] seem to give conflicting reports. It is assumed here that the MS is correct as the participant level data is given in the model. Therefore, just over 4% of each arm of the trial were still alive at the end of the study and there is a possibility this could have underestimated the survival benefit for either group.
- The use of the mean observed EQ-5D scores from both arms of the trial to take account of the missing EQ-5D data raises a number of problems. Utility in both groups of participants in the trial is unlikely to be the same throughout the cycles. The utility for topotecan participants early in the treatment cycles is likely to have been underestimated, as this is when the majority of BSC participants were progressing towards death. In the latter half of the treatment cycles the mean of the observed EQ-5D scores appear to have been overestimated, due to the small number of observations and as the proportion of healthier participants increases. It is not clear what effect this will have had on the model results.
- The assumptions over the costs in the model appear reasonable. Given that costs for the BSC arm of the trial were not recorded and that this component is common to both arms the conservative assumption may be justified However, a small percentage of palliative care costs are likely to have occurred in different periods for the topotecan and BSC and BSC alone groups and discounting could have been applied here.
- The description of how utilities were used in the model and the methods by which EQ-5D values were imputed to allow for missing data were not entirely clear in the MS.

4.2 SHTAC Independent economic assessment

Statement of the decision problem and perspective for the cost effectiveness analysis

We developed a new model to estimate the cost effectiveness of topotecan as a second-line chemotherapy compared with BSC, in a cohort of adults with relapsed SCLC for whom re-treatment with the first line regimen was not considered appropriate. The perspective of the cost effectiveness analysis is that of the NHS and PSS. The type of the economic evaluation was a cost-utility analysis. The health economic outcomes that are evaluated in the model are life years gained (LYGs) and QALYs gained. A discount rate of 3.5% was applied to both costs and benefits over the lifetime of the patients.

Strategies/comparators

The scope for the appraisal states that the interventions to be considered are oral and intravenous topotecan. The comparators for these interventions, including a comparison between the two interventions, are BSC, CAV and any other chemotherapy regimens.

The clinical effectiveness section above highlighted the different study populations that were used in the RCTs involving topotecan and relevant comparators (section 3.1.1). It was not felt appropriate to pool the RCTs identified. This resulted in the base case analysis of our economic model being limited to a comparison of oral topotecan with BSC and BSC alone, based on the O'Brien and colleagues study.[57] Furthermore, as noted in the MS, CAV is likely to be a more cost-effective option than topotecan as a second line chemotherapy for SCLC in patients for whom CAV is not contraindicated. Therefore, topotecan would only be used in a small subgroup of patients, where CAV was not considered appropriate as a second line chemotherapy. The base case analysis will consist of a comparison between oral topotecan with BSC compared to BSC alone.

A comparison of IV topotecan and BSC, based on an indirect comparison, was also attempted although with reservations (see section 4.2.2 below). This was undertaken to give a complete analysis of the use of topotecan (oral and IV) against BSC as a second line chemotherapy.

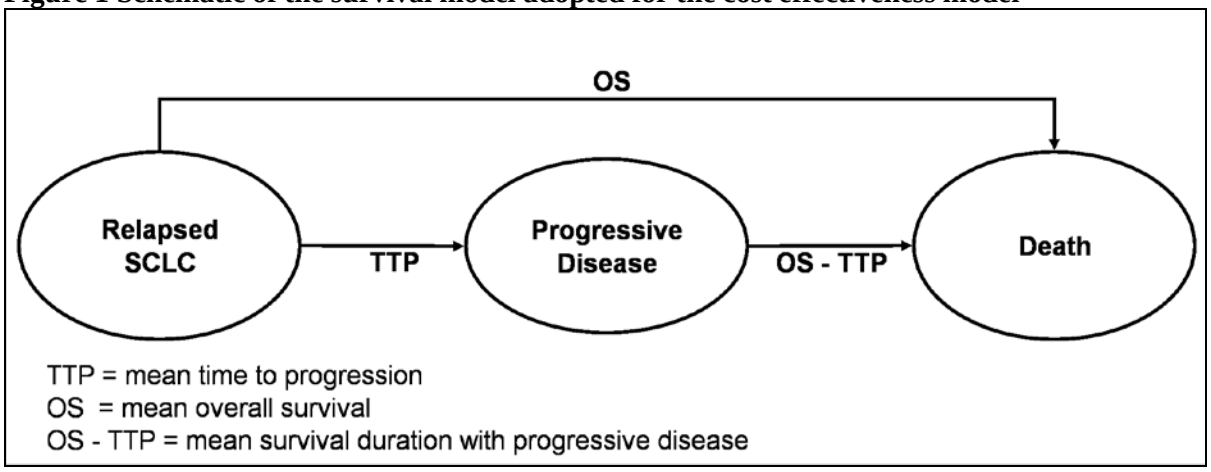
4.2.1 Methodology

Model type and rationale for model structure

Figure 1 presents a schematic of the basic survival model which, in its simplest form, contains three states – stable disease (i.e. patients' state at entry to the trial), progressive disease and death. Movements between these states are usually only permitted in the progressive direction. We have adopted this approach to model the cost effectiveness of topotecan as a second line chemotherapy.

Patients enter the model with relapsed SCLC, are unable or unwilling to undergo IV chemotherapy with CAV, and receive either BSC alone or topotecan with BSC. Patients may experience disease progression or may die without experiencing documented disease progression.

Figure 1 Schematic of the survival model adopted for the cost effectiveness model



The model uses data presented in the clinical effectiveness review (Section 3.1) and the MS to evaluate the most cost effective strategy for second line chemotherapy in SCLC. The model is fully probabilistic to take into account parameter imprecision. In addition, deterministic sensitivity analysis was used to explore different scenarios and assumptions in the model.

The base case analysis compared the mean overall survival for oral topotecan plus BSC ($meanOS_T$) with the mean overall survival for BSC ($meanOS_{BSC}$). The estimate of life years gained with the addition of oral topotecan to BSC (LYG_T), in the base case, was calculated as:

$$LYG_T = meanOS_T - meanOS_{BSC}$$

To estimate the QALY gain associated with the addition of oral topotecan to BSC ($QALYG_T$), treatment-specific utilities (U_T and U_{BSC} for oral topotecan plus BSC and for BSC respectively) reported by O'Brien and colleagues[57] and by Chen and colleagues,[64] were applied to the mean overall survival estimates. The quality adjusted life expectancy gain was therefore calculated as:

$$QALYG_T = meanOS_T * U_T - meanOS_{BSC} * U_{BSC}$$

This approach takes no account of the limited duration of follow up over which the utility data were collected. EQ-5D data were collected for 12 follow-up assessments (up to 36 weeks from randomisation, as stated in the MS), although the abstract by Chen and colleagues[64] reports that only data up to 12 weeks were included in the EQ-5D utility analyses. Therefore the utility data for patients in the oral topotecan and BSC arm may not reflect patients' QoL following disease progression. It has been noted elsewhere that there is likely to be a reduction in QoL when patients experience disease progression. As a result, an additional analysis was undertaken to explore the impact of the difference in QoL for patients following the development of progressive disease. The estimate of the QALY gain

associated with oral topotecan, taking into account the QoL impact of progressive disease, was calculated as:

$$QALYG_T = TTP_T*U_T + (meanOS_T - meanTTP_T)*U_{BSC} - meanOS_{BSC}*U_{BSC}$$

Baseline cohort

The baseline population in the economic model are adults with relapsed SCLC, for whom re-treatment with the first line regimen is not considered appropriate and who are unsuitable or unwilling to accept IV chemotherapy with CAV.

Discounting of future costs and benefits

A discount rate of 3.5% was applied to future costs and benefits in line with current guidance from NICE. Discount rates of 0% and 6% were applied in the sensitivity analysis.

Presentation of results of the base case model

We report the results of these comparisons in terms of incremental gain in QALYs and the incremental costs.

Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Parameter uncertainty is addressed using probabilistic sensitivity analysis. Probability distributions were assigned to the point estimates used in the base case analysis.

Deterministic sensitivity analysis is used to address particular areas of uncertainty in the model relating to:

- Model structure
- Methodological assumptions
- Parameters around which there is considerable uncertainty or which may be expected, *a priori,* to have a disproportionate effect on study results.

The purpose of this analysis is to identify clearly the impact of uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs.

4.2.2 Estimation of net benefits

Effectiveness data

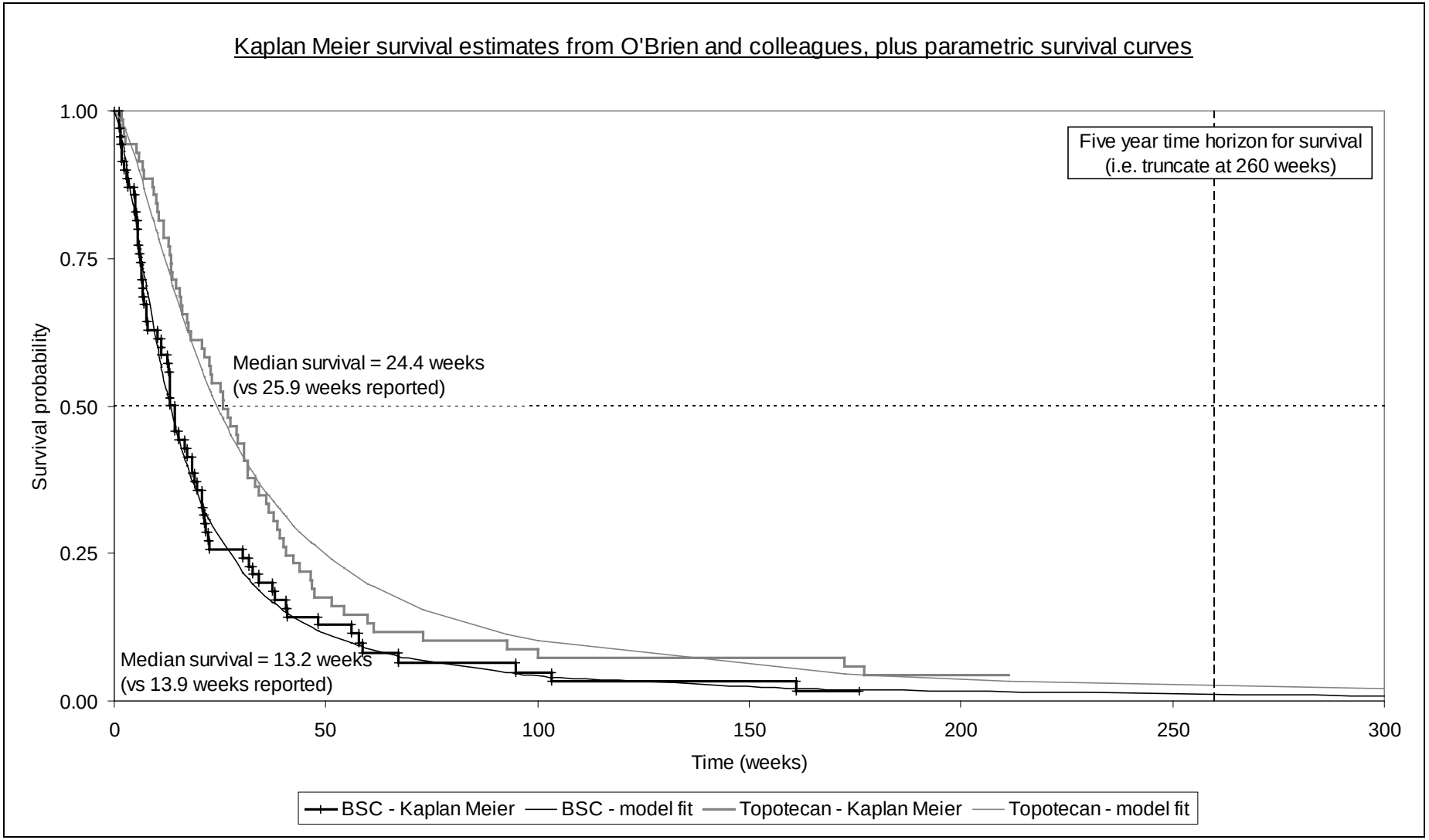
Oral topotecan plus BSC compared with BSC alone

The model builds upon the Kaplan-Meier curves for overall survival from the O'Brien and colleagues[57] study for topotecan with BSC and BSC alone. These survival curves were scanned using TechDig software and then imported into Microsoft Excel. In both arms, some of the participants remained alive at the end of the trial. Therefore, the final portions of the survival curves were

extrapolated using a regression analysis. A range of parametric survival functions were fit to the observed Kaplan Meier estimates (full details are included in Appendix 9). The log-logistic survival function provided the best-fit to the observed Kaplan Meier estimates and was used in the economic model.

The extrapolated survival curves are given in Figure 2 and compared to the Kaplan Meier survival estimates (details of the regression estimates are found in Appendix 9). These show a good fit to the overall survival curves. The most appropriate measure of overall survival is the mean rather than the median. Therefore, the associated mean survival times were estimated for the relevant survival curves.

Figure 2 Kaplan Meier survival estimates from the O'Brien and colleagues' trial and log-logistic fits



Mean survival (area under the survival curves) estimated directly from the Kaplan Meier survival function (truncated at the maximum observed survival for each arm in the RCT by O'Brien and colleagues[57]) and from the log-logistic survival functions (extrapolated to a maximum duration of five years) are reported in Table 25.

Table 25 Mean overall survival from Kaplan Meier and log-logistic survival functions

	Mean overall survival (years)	
Treatment Arm	Kaplan Meier estimate	Log-logistic function
Oral topotecan and BSC	0.7685	0.8271
BSC	0.4837	0.4864

The mean overall survival from the Kaplan Meier estimate and from the log-logistic function is very similar for BSC, at 0.4837 and 0.4864, respectively. For oral topotecan plus BSC, the mean overall survival from the log-logistic function is greater than the value based on the Kaplan Meier estimate by 0.06 years, or approximately three weeks. If the modelled survival function is truncated at the maximum survival duration observed in the RCT by O'Brien and colleagues,[57] the mean reduces to 0.7997 years. The difference between the modelled value and that estimated directly from the Kaplan Meier curve is reduced to approximately one and a half weeks.

The RCT by O'Brien and colleagues[57] did not report Kaplan Meier estimates for time to disease progression, but only reported the median TTP for oral topotecan and BSC. Moreover, no TTP data were reported for the BSC group (see section 3.1.3.1). To estimate the mean time to disease progression for oral topotecan plus BSC, the risk of disease progression was derived from the reported median TTP using an exponential approximation[72]

$$\lambda = -\ln(S)/t$$

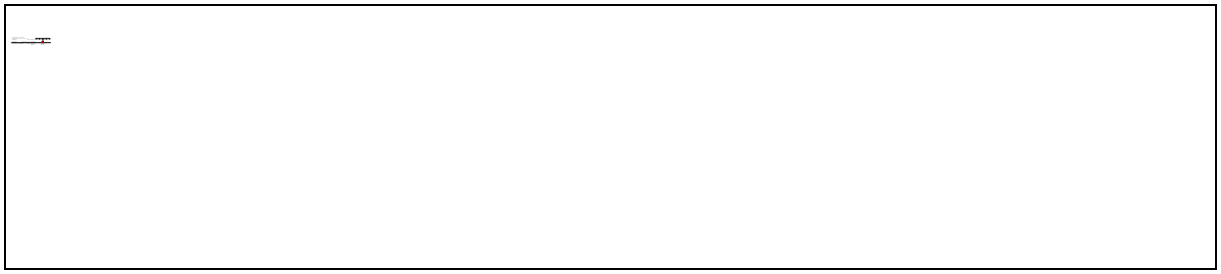
where S is the proportion of patients surviving (or in this case without disease progression) at time t. For the median TTP the value of S in the above equation is set, by definition, at 0.5, while t = 16.3 weeks (as presented in section 3.1.3.1 of this report). The mean TTP was calculated by taking the reciprocal of the risk of disease progression ($1/\lambda$), giving a value of 23.52 weeks. This approach has been used in previous Technology Assessment Reports (TARs) looking at second-line chemotherapies for ovarian cancer.[69] The accuracy of this estimate of the mean TTP depends on the adequacy of the exponential approximation, used to convert the median TTP to a risk of disease progression. The appropriateness of this transformation cannot be assessed without reference to the full survival function for time to disease progression, which has not been reported for the RCT by O'Brien and colleagues.[57] This represents a substantial source of uncertainty in the model. See Appendix 9 for additional analysis on TTP, using data from the MS.

Intravenous topotecan versus BSC

An analysis was undertaken to assess the effect of IV topotecan on overall survival, relative to BSC, based on an adjusted indirect comparison using data from three RCTs included in the review. Data from the RCT by O'Brien and colleagues[57] were used for the comparison of oral topotecan plus BSC against BSC alone, while the trials by Eckardt and colleagues[56] and von Pawel and colleagues[58] provided data for the comparison of oral topotecan with IV topotecan, as discussed in sections 3.1.3.1 and 3.1.3.3.

For the comparison of oral topotecan with IV topotecan, data on overall survival were available in the form of hazard ratios (Eckardt and colleagues[56]) and risk ratios (von Pawel and colleagues[58]). The point estimates and their 95% confidence intervals were entered into RevMan 5.0 software, and combined using the generic inverse variance method. In a fixed-effect meta-analysis there was no statistically significant difference between treatment arms (RR 0.95, 95% CI 0.76 to 1.17, p=0.62) see Figure 3. Heterogeneity was not statistically significant (p=0.56, I^2=0%).

Figure 3 Fixed-effect meta-analysis of relative risk of overall survival – oral versus intravenous topotecan.



Combining the pooled estimate with the hazard ratio for oral topotecan plus BSC compared with BSC alone reported by O'Brien and colleagues,[57] using the method for indirect comparison described by Glenny and colleagues,[73] gives a relative risk for overall survival with IV topotecan of 0.68 (95% CI 0.45 to 1.02) compared with BSC, see Table 26 below.

Table 26 Adjusted indirect comparison to derive the hazard ratio for overall survival for IV topotecan compared with BSC

	HR	ln(HR)	se(ln(HR))
Oral vs IV topotecan	0.95	-0.0541	0.1092
Oral topotecan vs BSC	0.64	-0.4463	0.1768
IV topotecan vs BSC	0.68	-0.3922	0.2078
The natural log of the hazard ratio for IV vs BSC is estimated by subtracting the natural log of the hazard ratio for Oral vs IV from the natural log of the hazard ratio for Oral vs BSC (-0.4463 - -0.0541 = -0.3922)			

This analysis is highly speculative, given the uncertainty whether these trials fully meet the inclusion criteria for this review (discussed in section 3.1.1), particularly regarding the comparability of participant populations in the RCTs and therefore the suitability of pooling their results.

Health state values/utilities

To calculate QALYs from the mean overall survival and mean time to progression, derived using the methods described above, it was necessary to adjust the survival times for QoL using appropriate utility or health state valuations.[67] As described in section 4.1.2, we found only limited data sources on QoL and health state utility for people with recurrent SCLC.

The utilities used in this analysis are based on those reported for the O'Brien and colleagues' RCT,[57] which used the EQ-5D in both trial arms (see section 3.1.3.1). Adopting these utility estimates has the advantage that they were derived:

- in a relevant population - those with SCLC who responded to first-line treatment, for whom retreatment with first line therapy is not considered appropriate and for whom BSC is an appropriate comparator strategy;
- using a measure and methodology (EQ-5D valued using a tariff derived from a representative sample of the general population) that is consistent with the NICE reference case.

In addition, it should be noted that our search for QoL studies and studies reporting utility estimates in this population failed to find any other relevant publications. However, there are shortcomings in the evidence base that need to be borne in mind:

- The QoL assessment within the trial is only reported very briefly in the main RCT publication.[57] There is very little detail on methods adopted for calculating utilities from the EQ-5D (the value set used is not reported), approaches to handling missing data (baseline data were collected for 96% of participants in the topotecan plus BSC arm and 93% in the BSC arm, while the proportions with at least one post-baseline assessment were 89% and 70% respectively); or methods used to estimate the rate of deterioration in scores over time.
- It is not clear how far the EQ-5D data, collected at three week intervals, captures the impact of treatment-related toxicity for those receiving oral topotecan.
- There was limited follow-up for the QoL assessments. The main trial publication does not report the duration of the QoL assessment. However the abstract by Chen and colleagues,[64] which reports the same rate of change from baseline to three months as the main trial publication,[57] states that the data analysed covered a maximum of 12 weeks from baseline (measures were administered at baseline and at four subsequent visits, occurring at three-week intervals). As a result these assessments are unlikely to capture the full impact of disease progression in the oral topotecan group.

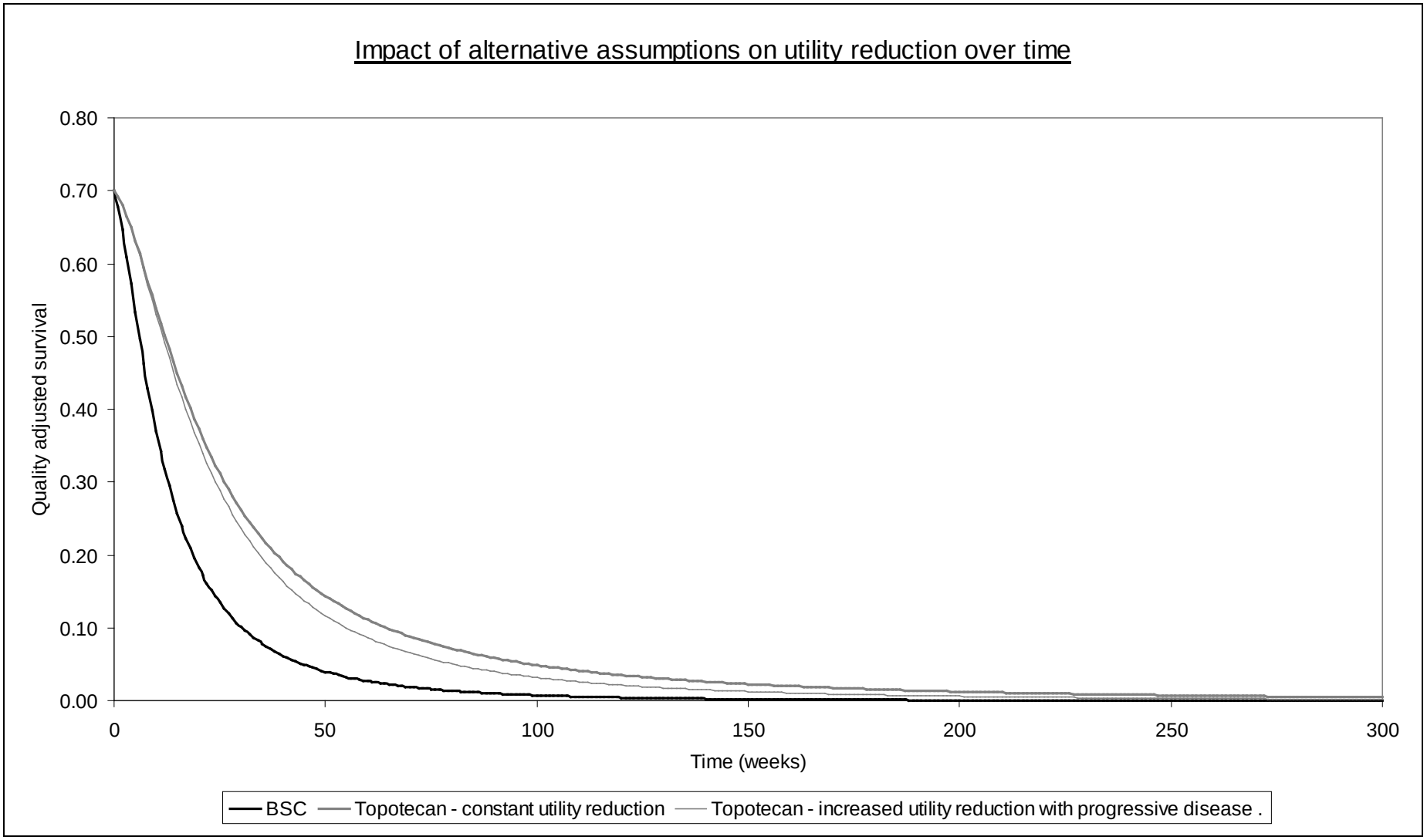
The RCT reported that the "rate of deterioration" in EQ-5D scores over three months was -0.05 for oral topotecan plus BSC and -0.20 for BSC alone. We interpreted this to indicate that, for each three-month period, the mean utility reduces from baseline by 5% for the oral topotecan plus BSC cohort and by 20% for the cohort receiving BSC alone.

Baseline EQ-5D values for all participants, or for each trial arm separately, were not reported in the main publication for the RCT by O'Brien and colleagues.[57] The abstract by Cheng and colleagues[64] reported a mean baseline utility (for patients in the RCT by O'Brien and colleagues) of 0.72 for oral topotecan plus BSC arm and 0.68 for BSC alone. These baseline values are for participants included in the pooled analysis (change from baseline to averaged on-treatment assessments). For the cost effectiveness model, we assume that the mean baseline utility for all participants is 0.7.

A regression analysis was used to infer the reduction of utility over time from the zero months and three months time points, and to model utility beyond the last observation and beyond the trial (see Appendix 11). In the base case, we assumed that any QoL reduction due to toxicity or adverse events would be picked up in the EQ-5D valuations from trial participants.

The base case analysis assumed that there was an associated loss of utility, in people treated with oral topotecan and BSC, once disease had progressed. This was assumed to be the same loss of utility that was associated with participants receiving BSC alone and was applied for survival durations beyond the estimated mean time to progression. Quality adjusted survival curves, showing the effect of assuming a greater reduction in utility following disease progression are shown in Figure 4.

Figure 4 Impact, on quality adjusted survival, of alternative assumptions regarding the utility reduction over time with topotecan



4.2.3 Estimation of net costs

Cost analysis

The cost data was based upon the resource use from the O'Brien and colleagues study.[57] This was supplemented from data from the MS and the other RCTs identified in the clinical effectiveness review. A questionnaire was also sent out to clinical experts to ascertain relevant costing and resource use associated with oral topotecan (see Appendix 13). All cost data and relevant sources are given and discussed in turn below.

Base case: Oral topotecan and BSC vs BSC alone

The groups of health care costs included in the base-case health economic model are drug costs, chemotherapy administration, on-treatment monitoring, cost of adverse events, post-treatment monitoring and palliative care costs.

Drug costs of oral topotecan

Oral topotecan is administered at 2.3 mg/m^2/day on five consecutive days of each 21-day course of treatment.[74] Table 27 reports the total dose per day of treatment for oral topotecan used in the cost effectiveness model. This assumes that patients have a body surface area (BSA) of 1.8 m^2 – this assumption is based on the BSA adopted by the SMC for costing IV topotecan for treatment of relapsed SCLC[47] – with the exact dosage (4.14 mg per day of treatment) rounded up to the nearest 0.25mg. This allows for the fact that some participants in the RCT by O'Brien and colleagues[57] experienced dose reductions (reported as 8% of courses) or dose escalations (reported as 14% of courses). Dose reductions and escalations occurred at increments of 0.4mg/m^2/day to a minimum dose of 1.5mg/m^2/day and to a maximum dose of 3.1mg/m^2/day. We estimated the mean oral topotecan dosages, allowing for dose reductions and escalations, to be between 2.29 and 2.38 mg/m^2/day (corresponding to dosages of 4.13 to 4.28 mg per day of treatment). These were calculated by weighting the standard dosage by the proportion of courses having dose reductions/ escalations and assuming that all reductions/ escalations were either one or two increments (i.e. either 0.4mg/m^2/day or 0.8mg/m^2/day).

Table 27 reports the unit costs, estimated cost per treatment day and cost per course for oral topotecan used in the cost effectiveness model. Unit costs for oral topotecan were taken from the current BNF (No 57, March 2009).[75] Oral topotecan is available on 10 capsule cards, with a unit cost of £300 per card of 1 mg capsules and £75 per card of 0.25 mg capsules.

The cost per course of oral topotecan has been calculated on the basis of no wastage – we assume that the hospital pharmacy department will supply patients with the exact quantity of capsules to deliver

the required dosage over each course of treatment. In the case of the patient with a BSA of 1.8 m^2 this would most closely be met by supplying twenty 1 mg capsules and five 0.25 mg capsules, which implies that the hospital pharmacy can supply fractions of the ten capsule card.

Table 27 Unit costs and cost per day of treatment with oral topotecan

Total dose per day of treatment	Cost per mg	Cost per day of treatment	Cost per course
4.25mg[†]	£30	£127.50	£637.50
[†] assume this is supplied by the hospital pharmacy as four 1mg capsules and one 0.25 mg capsules for each day of treatment within the current treatment course.			

The main trial publication[57] reports that a total of 278 treatment courses were delivered to the 71 participants randomised to oral topotecan (with a median of 4 per patient, range 1 to 10). In the cost effectiveness model we assume that people receive a mean of four courses of oral topotecan, which corresponds to a total drug cost per patient for oral topotecan of £2,550. This is similar to the mean cost per patient for oral topotecan of £2,500 reported in the MS.

Administration and monitoring costs for oral topotecan

The Summary of Product Characteristics (SmPC) for topotecan states that it should only be prescribed, and therapy should be supervised, by a physician experienced in the use of chemotherapeutic agents. We assumed that patients would attend the hospital once, at the beginning of each course, to collect the complete supply of oral topotecan for each course of treatment. At the same time patients would also receive a supply of an oral anti-emetic (domperidone, non-proprietary) and an anti-diarrhoeal (loperimide) to use as required. Patients attending the hospital to collect oral chemotherapy agents will also have their condition monitored. This will include a consultation with their treating physician (in which their medical history will be assessed for performance status, symptoms and for side effects of treatment) and a series of biochemical, haematological and imaging tests. We have assumed that the medical consultation will be accounted for under standard resource use assumptions for an outpatient attendance to receive oral chemotherapy. However, we have separately identified a set of tests required for patients undergoing chemotherapy with topotecan for relapsed SCLC. All patients will require a full blood count prior to administration of the first course of oral topotecan to ensure they have a baseline neutrophil count of $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of ≥ 9 g/dl (after transfusion if necessary).[74] In addition patients require a repeat of the full blood count, liver function tests, renal function tests (urea, creatinine and salts) and a chest X-ray (to assess tumour response) at each attendance. In addition, based on clinical advice, it was assumed that patients receiving active treatment would have a CT scan every two

cycles. Clinical advisors confirmed that these were appropriate resource use assumptions for the management of this group of patients.

The unit cost for an outpatient attendance to receive oral chemotherapy has been taken from NHS Reference Costs.[76] This does not include a pharmacy dispensing fee (which is included under procurement costs in NHS Reference Costs[77]). For the base case analysis we adopt the same pharmacy cost as in the MS, based on contract price per prescription for community pharmacists (£0.90 per prescription at 2007/08 prices). Unit costs for routine tests undertaken to monitor treatment-related toxicity and disease progression were provided finance department at Southampton University Hospitals Trust. Table 28 reports the unit costs adopted for costing the administration of oral topotecan and for patient monitoring while on treatment. Total cost per course is £274.14, comprising administration costs of £185.87 and monitoring costs of £88.28.

Table 28 Unit costs for administration of oral topotecan and for patient monitoring while on-treatment

Item	Unit cost (£)
Outpatient attendance to receive oral chemotherapy	184.97[†]
Pharmacy cost for dispensing oral chemotherapy	0.90*
FBC	2.90
LFT	4.70
U&E	4.70
Chest X-ray	28.64
CT scan (every 2 cycles)	47.34
Total cost per course of oral topotecan	274.14
Source for unit costs [†] NHS Reference Costs 2006/07, uprated to 2007/08 prices using Hospital and Community Health Services (HCHS) Pay and Prices Index[78] * Prescription Prescribing Authority. 2007/08 dispensing fee to community pharmacists, from MS[51] [‡] Finance Department, Southampton University Hospitals Trust	

Based on the unit cost assumptions in Table 28, costs for administration of oral topotecan and monitoring for the complete treatment duration of four courses of chemotherapy is £1097 (£743.47 for administration and £353.11 for monitoring).

Adverse events costs

The RCTs included in the clinical effectiveness review reported that treatment with oral topotecan was associated with both haematological and non-haematological adverse events.[56-58] The most common toxicities were haematological, with 61%, 38% and 25% of participants experiencing neutropenia, thrombocytopenia or anaemia, respectively, at grade 3 or 4 in the oral topotecan arm of

the RCT by O'Brien and colleagues[57] (see Section 3.1.3.1). Similar proportions were reported for trials including oral topotecan by Eckardt and colleagues[56] and by von Pawel and colleagues,[58] (see section 3.1.3.3). The proportion of participants with grade 3 and 4 non-haematological toxicities associated with treatment for oral topotecan was lower in the three trials, generally below 10% of patients.

O'Brien and colleagues[57] followed the usual convention of only reporting toxicity at grades 3 and 4, while the MS included non-haematological toxicity at all grades. Table 29 shows the proportion of participants, treated with oral topotecan, experiencing haematological toxicity, as reported by O'Brien and colleagues[57] and also in the MS. Table 29 also shows the proportion of cycles in which participants experienced haematological toxicity when treated with oral topotecan.

Table 29 Proportion of participants experiencing treatment-related haematological toxicity, as reported by O'Brien and colleagues[57] and in the clinical study report(CSR) submitted as part of the MS

Toxicity	Grade	Proportions of patients (O'Brien and colleagues)	Proportions of patients (from CSR)	Proportions of cycles (from CSR)
Neutropenia	3	61.2%	28.4%	16.4%
	4		32.8%	11.5%
Thrombocytopenia	3	37.7%	30.4%	11.4%
	4		7.2%	1.8%
Anaemia	3	24.6%	14.5%	5.1%
	4		10.1%	9.5%
Notes: Figures in column 4 are taken from the CSR for the RCT by O'Brien and colleagues, submitted as Appendix 5 of the MS, as there appears to be an error in Table 3.45 of the MS which reports the breakdown of haematological toxicity by grade.				

Table 30 (and Appendix 12) report the resource use assumptions adopted in our cost effectiveness model. Resource use assumptions adopted in a previous TAR for topotecan in the treatment of advanced ovarian cancer were updated, based on expert clinical opinion.

Table 30 Resource use assumptions for management of haematological adverse events. Unit cost assumptions and estimated cost per affected patient

Toxicity	Grade	Resource Use	Unit cost (£)	Cost per patient (£)
Neutropenia	3	Out-patient visit Amoxycillin	207.48[†] 1.37[‡]	103.74 0.69
	4	Inpatient admission (3.5 days) Piperacillin	249.83[†] 22.99[‡*]	874.41 321.86
Thrombocytopenia	3	No treatment		

	4	Day case admission Platelet transfusion Type and cross	367.29† 805.67 36.88	367.29 805.67 36.88
Anaemia	3	Day case admission Blood transfusion Type and cross	367.29† 90.05 36.88	367.29 90.05 36.88
	4	Day case admission Blood transfusion Type and cross	367.29† 535.60 36.88	367.29 535.60 36.88
Sepsis		Inpatient admission (10 days) 5 days in ICU 5 days on ward Piperacillin Clarithromycin Fluconazole IV	 1,022.86† 249.83† 22.99‡* 7.47‡ 29.28‡	 5,114.31 1249.15 459.80 10.70 204.96
† NHS Reference Costs 2006/07[76] uprated to 2007/08 prices using HCHS Pay and Prices Index[78] ‡ BNF, September 2008.[79] * unit cost for Piperacillin includes cost of 120ml saline for initial dilution and for IV infusion See Appendix 12 for full details of resource use assumptions and sources				

The most common grade 3/4 non-haematological adverse events occurring in the oral topotecan plus BSC arm of the RCT by O'Brien and colleagues[57] were diarrhoea, vomiting, fatigue and dyspnoea (see Table 31). The proportion of participants with grade 3 or 4 fatigue was the same in both arms of the trial and is not included in our model. Table 31 reports the breakdown of non-haematological toxicity between grades 3 and 4, taken from the CSR which was submitted as an appendix to the MS, and used in our cost effectiveness model. This table includes grade 3 nausea and grade 2 diarrhoea, which was not reported in the publication by O'Brien and colleagues.[57] We have included grade 2 diarrhoea in the model, following advice from clinical experts that this adverse event would require an outpatient attendance and prescription of further anti-diarrhoeal medication. We have assumed that grade 1 and 2 nausea and grade 1 diarrhoea occurring in patients treated with oral topotecan will be self-managed using the anti-emetic and anti-diarrhoeal medication supplied at the out-patient attendance which initiates each course of chemotherapy.

Table 31 Proportion of participants experiencing non-haematological toxicity, as reported by O'Brien and colleagues and in the CSR submitted as an appendix to the MS

Toxicity	Grade	Proportions reported by O'Brien and colleagues	Proportions reported in CSR
Diarrhoea	2	Not reported	12.9%
	3	6%	4.3%
	4		1.4%
Vomiting	3	3%	2.9%
	4		0.0%
Nausea	3	Not reported	1.4%

	4		0.0%
Notes: Figures in column 4 are taken from the Clinical Study Report for the RCT by O'Brien and colleagues, submitted as Appendix 5 of the MS. The main body of the MS did not report a breakdown of non-haematological toxicity by grade.			

Table 32 (and Appendix 12) present details of the cost per patient, as well as unit cost and resource estimates, for managing non-haematological toxicity for patients treated with oral topotecan. Clinical opinion was sought to validate these estimates which were based on assumptions adopted in a previous TAR which included topotecan (for advanced ovarian cancer[69]) and those developed for the MS.

Table 32 Resource use assumptions for management of non-haematological adverse events in the topotecan and BSC arm of the trial

Toxicity	Grade	Resource Use	Unit cost (£)	Cost per patient (£)
Diarrhoea	2	Outpatient visit	207.48†	207.48
		Loperamide	2.15‡	1.40
	3	Inpatient admission (5 days)	249.83†	1,249.15
		Loperamide	2.15‡	2.01
		Buscopan	2.59‡	2.59
		Codeine	0.97‡	0.97
	4	Inpatient admission (5 days)	249.83†	1,249.15
		Loperamide	2.15‡	2.01
		Buscopan	2.59‡	2.59
		Codeine	0.97‡	0.97
		Ciproflaxin IV	22.00‡	44.00
		Metronidazole IV	3.41‡	13.64
Nausea/Vomiting	3	Outpatient visit	207.48†	207.48
		Dexamethasone	3.27‡	13.08
		Granisetron	65.49‡	130.98
	4	Inpatient admission (5 days)	207.48†	1,037.39
		Dexamethasone IV	1.00‡	5.00
		Granisetron IV	26.69‡*	80.07
		Cyclizine	1.48‡	1.11

† NHS Reference Costs 2006/07[76]
uprated to 2007/08 prices using HCHS Pay and Prices Index[78]
‡ BNF, September 2008.[79]
* includes cost of 15ml saline for initial dilution
See Appendix 12 for full details of resource use assumptions and sources

Cost of non-progressive disease survival

In the base case model we assumed that patients have a mean duration of treatment of four courses of oral topotecan, which corresponds to 12 weeks. Patients are assumed to continue to attend out-patients for general medical care and for monitoring of their condition. This continued monitoring is costed in

the model until patients develop progressive disease. It is assumed that these patients will also have one chest X-ray and a CT to confirm disease progression.

The full package of care for patients during period from ceasing treatment with oral topotecan, until the development of progressive disease, is listed in Table 33 and consists of an out-patient visit, with full blood count every four weeks, and a GP consultation every four weeks. These correspond to a cost of £246.38 for each four week period prior to the development of disease progression. We adopted these assumptions based on information in the MS. Clinical experts were asked to comment on the appropriateness of these assumptions and whether there were any additional items of resource use for patients following the cessation of treatment with oral topotecan, and prior to the development of progressive disease, which should be included.

Table 33 Management costs for patients following cessation of treatment with oral topotecan, prior to disease progression.

Resource use item	Frequency of use	Unit cost
Out-patient attendance	Once every four weeks	207.48[†]
Full blood count		2.90[‡]
GP consultation	Once every four weeks	36.00*
Chest X-ray	Once, to confirm disease progression	28.64[†]
CT Scan		94.68[†]
Source for unit costs [†] NHS Reference Costs 2006/07, uprated to 2007/08 prices using Hospital and Community Health Services (HCHS) Pay and Prices Index[78] * Unit costs of Health and Social Care 2008[78]		

Assuming that mean time to progression is 23.52 weeks (derived, as described earlier in section 4.2.2.1 from the median TTP reported by O'Brien and colleagues[57]) and an average treatment duration of four courses we estimated that patients with SCLC, treated with oral topotecan, would have an average of 11.52 weeks from treatment cessation until disease progression. This corresponds to an average cost of continued monitoring, from treatment cessation until disease progression, of £709.57 per patient, plus £123.32 for imaging to confirm disease progression.

Cost of palliative care

BSC was available to participants in both arms of the RCT by O'Brien and colleagues[57] and involved the use of analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, RBC transfusions, deep relaxation therapy, and palliative radiotherapy or surgical procedures. The MS, and the main trial publication by O'Brien and colleagues,[57] generally provide little detail on the BSC components of care provided to participants in the trial (either for participants in the BSC arm or the

BSC component for participants receiving topotecan plus BSC). In particular there is no indication which components of treatment participants were receiving as palliative care. The MS and the trial publication[57] note a greater use of medication and radiotherapy in the BSC arm, while there were more blood transfusions for participants in the topotecan plus BSC arm (reflecting the high proportion of participants in this arm experiencing haematological toxicity).

Since BSC was common to both arms, and given that recording of resource use in the RCT was not comprehensive, the manufacturer's economic model did not include palliative care costs (justifying this as a conservative assumption that is most likely to over-estimate resource use for topotecan). However, while BSC is a common component in both arms, it is likely that participants will experience palliative care at different times in the two arms, given the survival advantage associated with topotecan. To assess the impact of this assumption, we include a published estimate of the cost of palliative care, derived in a retrospective analysis of case notes for 109 SCLC patients conducted in the UK.[49] The study estimated that 28% of the total costs of care occur after recurrence of the disease until death, of which 73% are generated by palliative care. The average cost of palliative care, for the 71 patients (65%) in the study cohort who received such care, was £3,495 at 1998 prices.

Table 34 Palliative care costs, and proportion each component contributes to total costs, inflated to 2007/08 prices.

Components costed in palliative care					Total
Hospitalisation	Outpatient visits	Tests and procedures	Surgery/ radiotherapy	Other	
£ 3,819 (77%)	£ 251 (5%)	£ 341 (7%)	£ 245 (5%)	£ 322 (6%)	£ 4,977
From Oliver and collagues[49]					

Summary of costs in SHTAC model

Table 35 reports a summary of the costs applied in the SHTAC base case model, broken down by categories of cost and are identified separately for the oral topotecan plus BSC and for the BSC groups.

Table 35 Breakdown of costs used in the SHTAC base case model for oral topotecan versus BSC

	BSC	Topotecan and BSC
Drug cost (per cycle)		637.50
Chemotherapy administration cost (per cycle)		185.87
Monitoring cost (per cycle)		88.28
Managing haematological adverse events (per cycle)		367.49
Managing non-haematological adverse events (per patient)		114.45
Non-progressive-disease survival (per day)		8.80[†]

Palliative care (per patient)	4,977	4,977
† a one-off cost £123.32 is also applied for imaging to confirm disease progression		

Sub analysis of IV topotecan vs BSC

Cost analysis

The categories of health care costs included in the model for IV topotecan are similar to those included for oral topotecan. The cost data were based upon resource use from the RCTs reported by Eckardt and colleagues[56] and von Pawel and colleagues,[58] supplemented by responses to the questionnaire sent to clinical experts (see Appendix 13).

Drug costs of IV topotecan

Intravenous topotecan is administered at 1.5 mg/m^2 per day on five consecutive days of each 21-day cycle. The powder for reconstitution and IV infusion is available in 1 mg and 4 mg vials, at unit costs of £97.65 and £390.62 repectively.[50] Table 36 reports the total dose per day of treatment for IV topotecan, assuming a BSA of 1.8 m^2. The total dosage per day cannot be delivered in exact multiples of 1 mg vials – in the base case we assumed that all excess was wasted. The impact of this assumption is tested in a sensitivity analysis, as are the potential impact of dose escalation and dose reductions.

IV topotecan is supplied as a powder, requiring reconstitution with saline (0.9% w/v sodium chloride intravenous infusion or 5% w/v glucose intravenous infusion) to a final concentration of between 25 and 50 mcg/ml. The unit cost of sodium chloride intravenous infusion was estimated as £0.06/mL, giving a total cost per day of treatment for IV topotecan of £298.95 and a cost per cycle of £1,494.75.

Table 36 Cost per day of treatment and cost per cycle with IV Topotecan

Total dose per day of treatment	IV topotecan cost per day of treatment†	Cost per cycle‡
2.70 mg	£298.95	£1,494.75
† Includes 100 mL 0.9% w/v sodium chloride intravenous infusion. The cost also assumes that three x 1 mg vials are used to deliver the required dosage, implying 0.3 mg is wasted. Assuming that the excess can be reused, the cost per day of treatment for exactly 2.70 mg would be reduced to £269.06. ‡ Assuming wastage. If the excess can be reused, the cost per cycle would reduce to £1,345.28.		

The 54 participants in the von Pawel and colleagues RCT[58] received a total of 213 courses of treatment. For the base case we assumed that patients would receive four cycles of treatment with IV topotecan, giving a total drug treatment cost of £5,979 (or £5,381.10 assuming reuse of excess).

Administration and monitoring costs for IV topotecan

We assumed that IV chemotherapy was administered in secondary care, on an outpatient basis, requiring five separate outpatient visits per cycle. The costs of outpatient visits for the administration

of chemotherapy were taken from NHS Reference Costs 2006/07 as detailed in Table 37. Pharmacy costs, for chemotherapy by simple IV infusion, were taken from a previous TAR (£23 at 2004/05 prices were up-rated to £25.44 using the HCHS Pay and Prices Index[78]).

Table 37 Unit costs for intravenous chemotherapy administration/ on-treatment monitoring and total costs per cycle for patients receiving IV topotecan

Item	Unit cost (£)
Outpatient attendance to receive IV chemotherapy (first attendance of cycle)	175.53†
Outpatient attendance to receive IV chemotherapy (subsequent attendances during cycle)	195.77‡
Pharmacy cost per cycle	25.44
FBC	2.90
LFT	4.70
U & E	4.70
Chest X-ray	28.64
CT scan (every 2 cycles)	47.34
Total cost per cycle	1,027.31
† HRG SB12Z: Deliver simple Parenteral Chemotherapy at first attendance ‡ HRG SB15Z:Deliver subsequent elements of a chemotherapy cycle source NHS Reference Costs 2006/07, uprated to 2007/08 prices using Hospital and Community Health Services (HCHS) Pay and Prices Index[78]	

On the basis of expert clinical opinion, on-treatment monitoring was assumed to be the same as for oral topotecan. The average cost per cycle was therefore £1,027.31 for IV topotecan administration. Assuming patients receive four cycles of treatment with IV topotecan this gives a total cost of £4,289.26 for IV chemotherapy administration and on-treatment monitoring, which breaks down as £3,936.15 for IV chemotherapy administration and £353.11 for on-treatment monitoring.

Adverse events costs IV topotecan

Relative risks for the incidence of adverse events with IV topotecan, compared with oral topotecan were estimated using data on the proportion of participants experiencing each adverse event from the RCTs by Eckardt and colleagues[56] and by von Pawel and colleagues[58] (see Table 18 and Table 19, section 3.1.3.3 for observed proportions and Appendix 14 for details of the calculation of the pooled estimates).

The proportion of patients receiving IV topotecan experiencing haematological toxicity in the model (reported in Table 38 below) was estimated by applying the pooled relative risks to the proportions of participants experiencing each grade of haematological toxicity in the O'Brien and colleagues RCT[57] (previously reported in Table 29).

Table 38 Estimated proportion of patients treated with IV topotecan experiencing haematological toxicity

Toxicity	Grade	Proportion experiencing toxicity
Neutropenia	3	27.8%
	4	48.0%
Thrombocytopenia	3	35.6%
	4	5.1%
Anaemia	3	22.1%
	4	6.1%
Sepsis		4.3%

Combining the above proportions with costs in Table 30 gives estimate of the cost of managing haematological adverse events for patients treated with IV topotecan of £1,105.

A similar approach was adopted for non-haematological adverse events – deriving relative risks from the RCTs comparing oral and IV topotecan and applying these to the proportions observed in the RCT by O'Brien and colleagues.[57] However, given the relatively lower incidence of non-haematological adverse events, there were a number of cases were no adverse events were reported (for example, no cases of Grade 2, 3 or 4 diarrhoea for IV topotecan and no cases of Grade 4 nausea for either arm were reported in the RCT by von Pawel and colleagues[58]). To take account of this, we increased the numerator and denominator by one – the shaded rows in the tables for non-haematological adverse events in Appendix 14 indicate which calculations included zero cells. The estimated proportion of patients receiving IV topotecan who experience non-haematological toxicity, in the model, are reported in Table 39.

Table 39 Estimated proportion of patients treated with IV topotecan experiencing non-haematological toxicity

Toxicity	Grade	Proportion experiencing toxicity
Diarrhoea	2	4.1%
	3	0.8%
	4	1.4%
Nausea	3	1.0%
	4	0.0%
Vomiting	3	1.4%
	4	0.0%

Combining the above proportions with the resource use assumptions listed in Table 32 gives an estimate of the cost of managing haematological adverse events for patients treated with IV topotecan of £45.

Cost of non-progressive disease survival IV topotecan

As with oral topotecan, we assume that patients continue to attend out-patients for general medical care and for monitoring of their condition after the completion of their course of treatment with IV topotecan. This continued monitoring is costed in the model until disease progression occurs. We assume that the components of this ongoing monitoring are the same as for patients receiving oral topotecan (see Table 33).

Estimates of the relative time to disease progression for IV topotecan in comparison with oral topotecan were derived using regression analysis of the Kaplan Meier estimates reported in von Pawel and colleagues[58] and Eckardt and colleagues[56] – these are reported in Appendix 15. The estimated mean time to progression using data from the RCT by von Pawel and colleagues,[58] where median TTP for IV topotecan was shorter than for oral topotecan, was 24.37 weeks. Taking into account the average treatment duration of four cycles of IV topotecan, this means that patients are expected to remain in the non-progressive disease state for 12.37 weeks following the end of treatment. This corresponds to an average cost of continued monitoring, from treatment cessation until disease progression, of £885, including for imaging to confirm disease progression. Alternatively, using data from the RCT by Eckardt and colleagues,[56] in which the median TTP for IV topotecan was longer than for oral topotecan, the estimated mean time to progression was 32.07 weeks. This means that patients are expected to remain in the non-progressive disease state for 20.07 weeks following the end of treatment, giving an average cost of £1,360.

Cost of palliative care

Costs of palliative care were assumed to be the same as for BSC and oral topotecan, see Table 34.

Summary of costs in SHTAC model

Table 40 reports a summary of the cost per patient, applied in the SHTAC base case model. The total costs are broken down by categories of cost and are identified separately for the oral topotecan plus BSC and for the BSC alone groups.

Table 40 Breakdown of costs used in the SHTAC base case model for IV topotecan versus BSC

	BSC (£)	IV Topotecan and BSC (£)
Drug cost (per cycle)		1,494.75

Chemotherapy administration cost (per cycle)		984.04
Monitoring cost (per cycle)		88.28
Managing haematological adverse events (per patient)		1,104.57
Managing non-haematological adverse events (per patient)		44.62
Non-progressive-disease survival (per day)		8.80†
Palliative care (per patient)	4,977	4,977
† a one-off cost £123.32 is also applied for imaging to confirm disease progression		

Summary of the SHTAC cost-effectiveness model

- The cost effectiveness model was developed using a survival model methodology.
- The model includes three states – relapsed SCLC, progressive disease and death. No data on TTP in the BSC alone group were collected. TTP for oral topotecan was included in the model, to allow for poorer QoL with disease progression. QoL weights applied to the BSC group, were applied to oral topotecan patients once they have progressive disease.
- The survival model was developed using the published Kaplan Meier estimates for overall survival and TTP data included in the MS.
- Utility values reported by O'Brien[57] and colleagues and by Chen and colleagues[64] were used in the model. Limited published data are available on these QoL values and full details of the methods used to analyse these data are not available in published sources. Limited extra detail was identified in the MS. QoL values were estimated by applying the rate of deterioration, reported by O'Brien and colleagues and by Chen and colleagues,[64] to the baseline EQ-5D utility value for participants included in the RCT by O'Brien and colleagues.[57]
- Resource use associated with oral and IV topotecan were estimated from included RCTs, the MS and using advice from clinical experts. Where insufficient detail for estimating resource use or costs was available in included studies or the MS (particularly for palliative care) appropriate costs were taken from published sources. Where available, drug costs were taken from the BNF. Other unit costs were taken from NHS reference costs, Southampton University Hospitals Trust or published sources. The cost base for the evaluation was the 2007/08 financial year – where costs were taken from other cost years, these were adjusted using the HCHS Pay and Prices Index.
- The base case model has a five year time horizon. Alternative scenarios, truncating the survival functions at the maximum follow up in the RCT (for oral topotecan) or adopting a longer (ten year) horizon, are included in sensitivity analyses to assess whether extrapolation using survival function is likely to introduce bias. Alternative forms of survival function were investigated to determine whether this introduced bias.
- Discount rates at 3.5% for costs and outcomes are applied.

4.2.4 Estimation of cost-effectiveness

Cost effectiveness of topotecan – base case analysis

This section reports cost effectiveness results for a cohort of patients with relapsed SCLC, for whom re-treatment with the first line regimen is not considered appropriate and who are unsuitable or unwilling to accept IV chemotherapy with CAV, as discussed in section 4.2.1. Discounted costs (identifying the contribution of drugs, drug administration and monitoring while receiving oral topotecan, management of adverse events, monitoring prior to disease progression and palliative care) are presented alongside the life expectancy and quality adjusted life expectancy for patients in the cohort. The results are presented as incremental cost per life year gained and incremental cost per QALY gained.

Costs and outcomes modelled for cohorts of patients receiving oral topotecan plus BSC or BSC alone are presented in Table 41. Costs and health outcomes in the table have been discounted at 3.5%.

Table 41 Base case analysis

Treatment	Costs (£)	Life years	Incremental cost per life year gained (£)	QALYs	Incremental cost per QALY gained (£)
BSC	4,854	0.4735		0.2247	
Oral topotecan and BSC	11,048	0.7984	19,065	0.4077	33,851

The estimated gain in discounted life expectancy, associated with the addition of oral topotecan to BSC, is 0.3249 years (16.9 weeks). The equivalent undiscounted values are 0.3407 years (17.7 weeks). The estimated gain in discounted QALYs, associated with the addition of oral topotecan to BSC, is 0.1830. The equivalent undiscounted value is 0.1894 QALYs.

The incremental cost, associated with the addition of oral topotecan to BSC, is £6,194. Table 42 reports a breakdown of treatment costs, by phase of treatment, for each cohort. Palliative care is the only phase of treatment identified for patients receiving BSC alone, and this represents 100% of the treatment cost for this cohort. In contrast, for patients receiving treatment with oral topotecan in addition to BSC, while palliative care remains the single most costly phase these have reduced to 43% of total costs for this cohort. Active treatment with oral topotecan (including drug administration and on-treatment monitoring in addition to the costs of the drug itself) represents 33% of total costs for this cohort, with drug costs constituting 70% of active treatment costs. Other significant contributions to total costs for the oral topotecan and BSC cohort are costs of managing haematological toxicity (13%) and monitoring for disease progression in patients following cessation of treatment (10%).

Table 42 Treatment costs by phase of treatment

Phase of treatment		Oral Topotecan (£)	BSC (£)
Active treatment	Drug	2,550	
	Drug administration	743	
	On-treatment monitoring	353	
Adverse event costs	Haematological	1,470	
	Non-Haematological	114	
Non-progressive disease monitoring		1,082	
Palliative care		4,735	4,854
Total		11,048	4,854

Oral topotecan as a treatment for patients with relapsed SCLC, for whom re-treatment with the first line regimen, is not considered appropriate is associated with both improved outcomes (in terms of life expectancy and quality-adjusted life expectancy) and increased costs. QALY outcomes have increased by approximately 80% while costs have more than doubled, yielding an incremental cost effectiveness ratio for the addition of oral topotecan to BSC of £33,851 per QALY gained.

Cost effectiveness of topotecan –deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around the model structure and for variation in certain key parameters that were expected, *a priori*, to be influential on the cost-effectiveness results. The method adopted in most cases was univariate sensitivity analysis. That is, varying one parameter at a time, leaving all other variables unchanged. This is to highlight the impact, if any, of each selected parameter alone on the cost-effectiveness results. In some situations (such as the analysis of alternative parametric forms for the survival function, or the analysis using the upper confidence limits for all parameters in survival model) a set of related parameters are varied simultaneously. The effects of uncertainty in multiple parameters were addressed using probabilistic sensitivity analysis, which is reported later in the section.

Table 43 reports the results of the sensitivity analysis. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using a five year time horizon. The table is divided to distinguish between analyses undertaken due to uncertainties over structural assumptions in the model, methodological uncertainties (in this case related to the discount rates applied in the model) and uncertainty over parameter values. Where unit costs have been taken from NHS Reference Costs, the upper and lower quartiles have been used in the sensitivity analysis. In all other cases unit costs have been varied by plus or minus 20%. To test the sensitivity of the cost effectiveness results to assumptions over the method of estimating adverse event costs, the proportion of patients experiencing adverse events (rather than the proportion of cycles in which adverse events occurred) were used to estimate adverse event costs. In the assessment report by Main and colleagues[69] the same

transfusion cost was applied for patients experiencing grade 3 and grade 4 anaemia. Clinical advice suggested that patients experiencing grade 4 anaemia would require four units of blood – this was costed in the base case. The final entry in the table shows the cost effectiveness results using the transfusion cost from Main and colleagues.[69]

Table 43 Deterministic sensitivity analysis

	Cost (£)	Life years gained	QALYs gained	ICER (£ per QALY gained)
Base case	6,194	0.3249	0.1830	33,851
Structural assumptions				
Truncate survival at maximum follow up for trial	6,160	0.3202	0.1806	34,114
Extrapolate overall survival up to ten years	6,302	0.3596	0.1871	33,681
Weibull survival and TTP model	5,940	0.3144	0.1591	37,338
Methodological assumptions				
Discount rates (0% for both costs and outcomes)	6,283	0.3407	0.1894	33,177
Discount (6% for costs and 1.5% for outcomes)	6,136	0.3337	0.1866	32,889
Parameter uncertainty				
Lower 95% CI for treatment effect	6,183	0.3514	0.1909	32,381
Upper 95% CI for treatment effect	6,204	0.2991	0.1751	35,432
Lower 95% CI for all parameters in survival model	6,144	0.4124	0.2009	30,579
Upper 95% CI for all parameters in survival model	6,229	0.2536	0.1660	37,515
Lower 95% CI for all parameters in TTP model	6,961	0.3249	0.2360	29,496
Upper 95% CI for all parameters in TTP model	5,676	0.3249	0.1516	37,454
Exclude palliative care costs	6,313	0.3249	0.1830	34,502
Lower limit for utility values	6,194	0.3249	0.1498	41,346
Upper limit for utility values	6,194	0.3249	0.2492	24,859
No adjustment to utility for oral topotecan cohort post-progression	6,194	0.3249	0.2442	25,364
Round down oral topotecan dosage	6,044	0.3249	0.1830	33,031
Use proportion of patients with adverse events	5,703	0.3249	0.1830	31,166
Cost of out-patient visit to administer oral chemotherapy: lower quartile	5,714	0.3249	0.1830	31,227
Cost of out-patient visit to administer oral chemotherapy:upper quartile	6,472	0.3249	0.1830	35,373

	Cost (£)	Life years gained	QALYs gained	ICER (£ per QALY gained)
Cost of palliative care reduced by 20%	6,313	0.3249	0.1830	34,502
Cost of palliative care increased by 20%	6,313	0.3249	0.1830	34,502
Cost of out-patient visit for monitoring: lower quartile	5,858	0.3249	0.1830	32,017
Cost of out-patient visit for monitoring: upper quartile	6,395	0.3249	0.1830	34,949
Cost (per day) of in-patient admission: lower quartile	6,015	0.3249	0.1830	32,871
Cost (per day) of in-patient admission: upper quartile	6,300	0.3249	0.1830	34,432
Cost of day-case admission: lower quartile	6,100	0.3249	0.1830	33,335
Cost of day-case admission: upper quartile	6,294	0.3249	0.1830	34,396
Use transfusion cost from Main and colleagues[69] for Grade 4 anaemia	6,025	0.3249	0.1830	32,927

The cost effectiveness results appear to be generally robust to variation in the parameters included in the deterministic sensitivity analysis, with ICERs varying between approximately £30,000 and £37,000 per QALY gained. Among the structural sensitivity analyses, the results appear to be most sensitive to assumptions over the functional form for the survival functions. In terms of parameter inputs, the results appear to be most sensitive to variation in utility estimates applied in the model, variation in values of parameters in the survival functions (for overall survival and time to progression) and to the cost of outpatient attendance for the administration of oral chemotherapy.

Time horizon for the model appears to have a very limited impact on the cost effectiveness estimates. Truncating survival at the maximum duration observed for each arm in the O'Brien and colleagues RCT[57] reduces the QALY gain by 0.0024 and costs by £34. The proportionate reduction in outcome (1.3%) is greater than the proportionate reduction in costs (0.5%) hence the ICER increases, but only by a small amount. Increasing the maximum survival duration to ten years has the opposite effect – a slight increase in QALY gain and a slight increase in costs, with the proportionate change in QALYs being greater than the proportionate increase in costs, leading to a small reduction in the ICER. Adopting an alternative (Weibull) parametric form for the overall survival and TTP survival functions has a more dramatic effect, resulting in a 13% reduction in QALY gain, a smaller reduction in cost, and an increase in the ICER to £37,338.

Varying the discount rates applied has comparatively little effect. Zero discount rates for costs and outcomes result in slight increases in both incremental cost and incremental QALYs compared with

baseline values. Applying discount rates of 6% for costs and 1.5% for outcomes leads to a slight reduction in incremental cost and to an increase in incremental QALYs. The resulting ICER is slightly lower than in the base case.

Varying the value of the treatment effect parameter in the overall survival model, between its upper and lower confidence limits, has a greater effect on outcomes than on cost. In the model, variation in survival (unless it is assumed to be associated with variation in TTP) only has an impact on the duration of post-progression survival, and therefore will only affect the estimate of palliative care costs. A similar situation applies to QALY outcomes where, it is assumed that all gains or losses of life expectancy associated with variation in the treatment effect parameter are weighted by post-progression utility values. This explains why the proportionate variation in QALY gains in less than the variation in life years gained.

The cost effectiveness results are more variable if all parameters in the survival models are included (at the 95% confidence limits) in the sensitivity analysis, rather than just the treatment effect estimated in the overall survival model, with ICERs varying between approximately £30,000 and £37,500 per QALY gained. Variation in the parameters of the TTP survival model has a particularly large impact on incremental cost. This arises from the inclusion of a cost of approximately £9 per day (£246 every four weeks) to monitor disease progression in patients following treatment with oral topotecan (see Table 33 and accompanying text for assumptions).

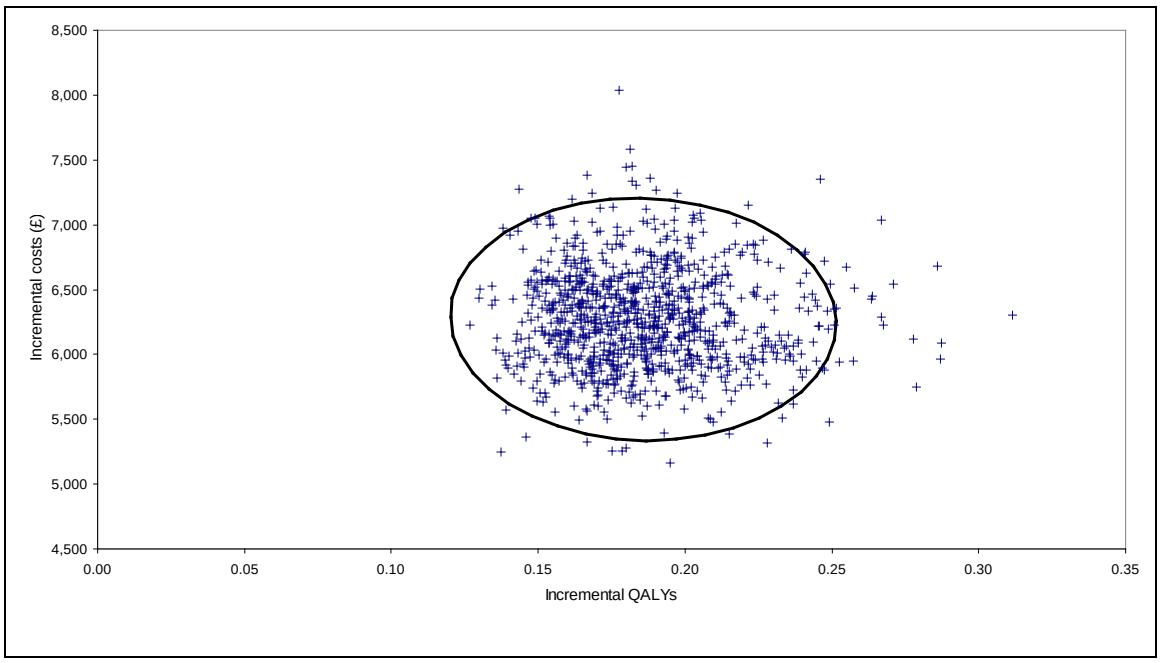
The greatest variation in cost effectiveness results, associated with parameter inputs, is related to the rate of deterioration in utility values over time. Using the lower 95% confidence limits as an estimate of the higher rate of deterioration (-0.11 for oral topotecan plus BSC, -0.27 for BSC alone, see Table 5) leads to a reduction of 0.03 (18%) in the QALY gain associated with oral topotecan and BSC. As a result the ICER increases to £41,346 per QALY gained. In contrast, using the upper 95% confidence limits, giving a lower rate of deterioration (0.02 for oral topotecan and BSC, -0.12 for BSC alone, see Table 5) leads to an increase of 0.07 (36%) in the QALY gain associated with oral topotecan and BSC, with the ICER reducing to £24,859 per QALY gained. To test the sensitivity of the cost effectiveness results to the assumption that the QoL deterioration for the oral topotecan and BSC cohort would be significantly greater following disease progression, the utility adjustment for post-progression survival was removed. This meant that the same rate of deterioration (-0.05 reported for oral topotecan and BSC, see Table 5) was applied for both pre- and post-progression survival. The increase in the incremental QALY gain was almost as great as for the sensitivity analysis using the upper 95% confidence limits, with the ICER reducing to £25,364, compared with the base case.

In terms of cost parameters, the model results appear to be most sensitive to variation in the cost of outpatient attendances for the administration of oral chemotherapy. This is unsurprising as these represent the majority of the administration costs for oral topotecan, and administration cost constitute 7% of total costs for the oral topotecan and BSC cohort.

Cost effectiveness of topotecan – probabilistic analysis

In a probabilistic sensitivity analysis, where the parameters of the survival models (both overall survival and TTP) probabilities of adverse events, proportionate deterioration in health state utility values, cost of outpatient attendances and patient monitoring, as well as costs of managing adverse events and palliative care were sampled probabilistically, oral topotecan plus BSC is associated with increased QALYs (with a range from 0.13 to 0.31 QALYs), but also increased costs (from £5,160 to £8,040) in all simulations when compared with BSC alone (see Figure 5, which also shows the 95% confidence ellipse).

Figure 5 Cost effectiveness plane – incremental cost and incremental QALYs for oral topotecan compared with BSC



The distributions assigned to each variable included in the probabilistic sensitivity analysis and the parameters of the distribution are reported in Appendix 10. One thousand simulations were run for this analysis. The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis (see Table 41 for the base case analysis). Table 44 reports the mean costs and outcomes from the probabilistic analysis (including the 2.5th and 97.5th

percentiles to give an indication of the range of the simulated values) and the ICER for oral topotecan plus BSC compared with BSC alone, based on the mean values generated in the probabilistic analysis.

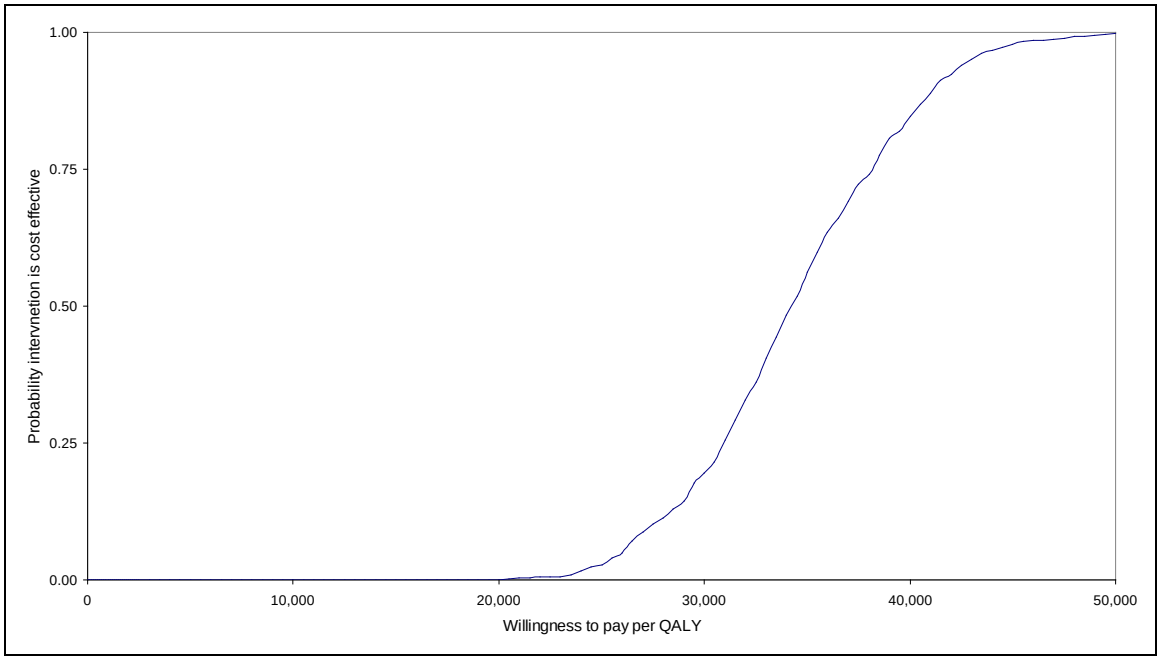
Table 44 Costs and outcomes from probabilistic analysis for oral topotecan and BSC

	Discounted costs			Discounted QALYs			
	Mean	2.5th Percentile	97.5th Percentile	Mean	2.5th Percentile	97.5th Percentile	ICER
BSC	4,882	2,186	8,584	0.2258	0.2047	0.2522	
Oral topotecan and BSC	11,153	8,394	14,813	0.4116	0.3672	0.4732	33,753

The ICER reported in Table 44, calculated using the difference in mean discounted costs and mean discounted QALYs shown in the table, is slightly lower than the mean of the ICERs calculated at each simulation (which was £34,430).

In addition to graphing the incremental cost and incremental QALYs for oral topotecan plus BSC, a cost effectiveness acceptability curve was derived, representing the proportion of simulations where oral topotecan treatment is cost effective for a range of willingness to pay thresholds, up to £50,000, see Figure 6. In this analysis oral topotecan plus BSC had a probability of being cost-effective of 0% at a willingness to pay threshold of £20,000 per QALY, 20% at a willingness to pay threshold of £30,000 per QALY and 100% at a willingness to pay threshold of £50,000 per QALY.

Figure 6 Cost effectiveness acceptability curve for oral topotecan and BSC



Cost effectiveness of IV topotecan

This section reports cost effectiveness results for a cohort of patients with relapsed SCLC, for whom re-treatment with the first line regimen is not considered appropriate and who may be suitable for treatment with IV topotecan. As for oral topotecan, discounted costs (identifying the contribution of drugs, drug administration and monitoring, management of adverse events, monitoring prior to disease progression and palliative care) are presented alongside the life expectancy and quality adjusted life expectancy for patients in the cohort. The results are presented as incremental cost per life year gained and incremental cost per QALY gained relative to BSC.

Costs and outcomes modelled for cohorts of patients receiving IV topotecan and BSC or BSC alone are presented in Table 45, based on the indirect comparison for overall survival described in section 4.2.2, time to progression as described in Appendix 15 and relative risks of adverse events (compared with oral topotecan) described in Appendix 14. Costs and health outcomes in the table have been discounted at 3.5%.

Table 45 Cost effectiveness results for IV topotecan compared with BSC

Treatment	Costs (£)	Life years	Incremental cost per life year gained (£)	QALYs	Incremental cost per QALY gained (£)
BSC	4,854	0.4735		0.2247	
IV topotecan and BSC	16,914[†] 17,369[‡]	0.7784	39,552[†] 41,043[‡]	0.3875[†] 0.4157[‡]	74,074[†] 65,507[‡]

[†] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by von Pawel and colleagues[58]
[‡] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by Eckardt and colleagues[56]

The estimated gain in discounted life expectancy, associated with the addition of IV topotecan to BSC, is 0.3049 years (15.9 weeks) – approximately one week shorter than the life expectancy gain in the base case analysis for oral topotecan, reported above. The equivalent undiscounted values are 0.3196 years (16.6 weeks). As noted in Appendix 15, the two RCTs comparing oral and IV topotecan give contradictory results on the relative TTP. This has no effect on the estimated life year gain with IV topotecan. However, given the assumption of a higher rate of deterioration in QoL following disease progression (see section 4.2.2.1), this has an effect on the QALY gain. The estimated gain in discounted QALYs, associated with the addition of IV topotecan to BSC, is 0.1628, when time to progression is modelled using data from the RCT by von Pawel and colleagues,[58] and 0.1910, when time to progression is modelled using data from the RCT by Eckardt and colleagues.[56] The equivalent undiscounted values are 0.1683 and 0.1981 QALYs, respectively.

The incremental cost, associated with the addition of IV topotecan to BSC, is substantially higher than for oral topotecan - £12,060, when TTP is modelled using data from the RCT by von Pawel and colleagues[58] and £12,514, when TTP is modelled using data from the RCT by Eckardt and colleagues.[56] Table 46 reports a breakdown of treatment costs, by phase of treatment, for each cohort. For patients receiving treatment with IV topotecan, palliative care is no longer the most costly phase (reduced to 27% of total costs) for this cohort, while the costs of active treatment with topotecan comprise 58% of total costs (35% drug costs and 23% for chemotherapy administration).

Table 46 Treatment costs by phase of treatment

Phase of treatment		IV Topotecan (£)	BSC (£)
Active treatment	Drug	5,979	
	Drug administration	3,936	
	On-treatment monitoring	353	
Adverse event costs	Haematological	1,132	
	Non-Haematological	45	
Non-progressive disease monitoring		726[†] 1,181[‡]	
Palliative care		4,743	4,854
Total		16,914[†] 17,369[‡]	4,854

[†] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by von Pawel and colleagues[58]
[‡] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by Eckardt and colleagues[56]

IV topotecan as a treatment for patients with relapsed SCLC, for whom re-treatment with the first line regimen is not considered appropriate, is associated with improved outcomes (in terms of life expectancy and quality-adjusted life expectancy) over BSC and similar outcomes to oral topotecan. However these outcomes are achieved at substantially greater cost – the ICER for IV topotecan compared with BSC is £74,074 per QALY gained, when time to progression is modelled using data from the RCT by von Pawel and colleagues[58] and £65,507 per QALY gained, when time to progression is modelled using data from the RCT by Eckardt and colleagues.[56] IV topotecan is strictly dominated by oral topotecan (poorer outcomes at higher cost), when time to progression is modelled using data from the RCT by von Pawel and colleagues[58] and has an ICER of £783,734 per QALY gained compared with oral topotecan, when time to progression is modelled using data from the RCT by Eckardt and colleagues.[56]

Cost effectiveness of IV topotecan – deterministic sensitivity analysis

Table 47 reports the results of a deterministic sensitivity analysis for IV topotecan. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using a five year time horizon. The table is divided to distinguish between analyses undertaken due to uncertainties over structural assumptions in the model, methodological uncertainties (in this case related to the discount rates applied in the model) and uncertainty over parameter values. The upper value in each cell of Table 47 gives the incremental costs, life years gained, QALYs gained and ICER using TTP based on data from the RCT by Eckardt and colleagues,[56] while the lower value is based on TTP from the RCT by von Pawel and colleagues.[58]

Table 47 Deterministic sensitivity analysis

	Cost (£)	Life years gained	QALYs gained	ICER (£ per QALY gained)
Base case	12,514 12,060	0.3049	0.1910 0.1628	65,507 74,074
Structural assumptions				
Extrapolate overall survival up to ten years	12,638 12,149	0.3371	0.1962 0.1660	64,425 73,182
Methodological assumptions				
Discount rates (0% for both costs and outcomes)	12,611 12,137	0.3196	0.1981 0.1683	63,674 72,134
Discount (6% for costs and 1.5% for outcomes)	12,452 12,009	0.3131	0.1950 0.1659	63,868 72,408
Parameter uncertainty				
Lower 95% CI for treatment effect	12,504 12,050	0.3296	0.1985 0.1703	62,984 70,755
Upper 95% CI for treatment effect	12,524 12,069	0.2809	0.1836 0.1554	68,200 77,664
Lower 95% CI for all parameters in survival model	12,468 12,013	0.387	0.2081 0.1799	59,919 66,796
Upper 95% CI for all parameters in survival model	12,547 12,092	0.2381	0.1755 0.1468	71,484 82,390
Relative treatment effect of IV vs oral (lower limit)	12,542 12,087	0.2346	0.1691 0.1408	74,176 85,831
Relative treatment effect of IV vs oral (upper limit)	12,476 12,021	0.3975	0.2186 0.1904	57,063 63,135
Lower 95% CI for all parameters in TTP model	13,376 12,725	0.3049	0.2815 0.2066	47,514 61,581
Upper 95% CI for all parameters in TTP model	11,929 11,614	0.3049	0.1539 0.1371	77,487 84,689
Exclude palliative care costs	12,626 12,171	0.3049	0.1910 0.1628	66,089 74,756
Lower limit for utility values	12,514 12,060	0.3049	0.1551 0.1343	80,705 89,767

	Cost (£)	Life years gained	QALYs gained	ICER (£ per QALY gained)
Upper limit for utility values	12,514 12,060	0.3049	0.2643 0.2187	47,347 55,144
No adjustment to utility for oral topotecan cohort post-progression	12,514 12,060	0.3049	0.2335 0.2335	53,585 51,638
Cost of out-patient visits to administer IV chemotherapy: lower quartile	10,522 10,067	0.3049	0.1910 0.1628	55,076 61,833
Cost of out-patient visits to administer IV chemotherapy:upper quartile	13,852 13,398	0.3049	0.1910 0.1628	72,510 82,291
Cost of palliative care (reduced by 20%)	12,542 12,087	0.3049	0.1910 0.1628	65,653 74,244
Cost of palliative care (increased by 20%)	12,487 12,032	0.3049	0.1910 0.1628	65,362 73,903
Cost of out-patient visit for monitoring: lower quartile	12,132 11,819	0.3049	0.1910 0.1628	63,507 72,594
Cost of out-patient visit for monitoring: upper quartile	12,743 12,204	0.3049	0.1910 0.1628	66,705 74,960
Use transfusion cost from Main and colleagues[69] for Grade 4 anaemia	12,487 12,033	0.3049	0.1910 0.1628	65,366 73,908

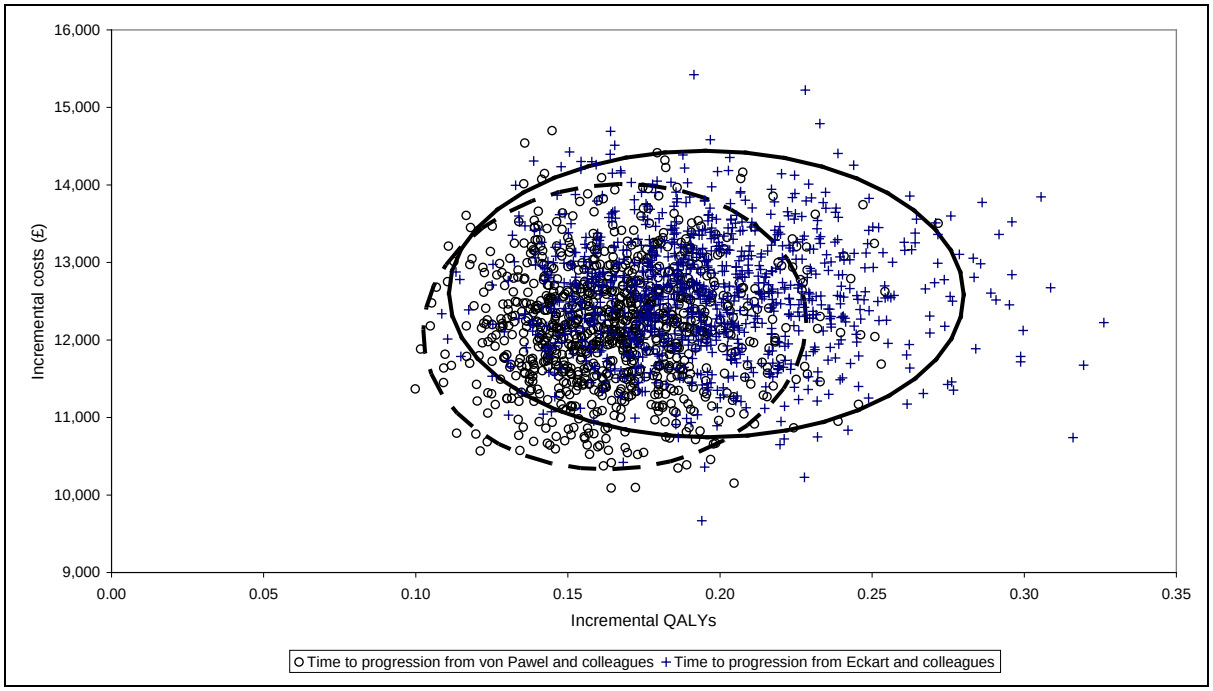
The cost effectiveness results appear to be generally robust to variation in the parameters included in the deterministic sensitivity analysis, with ICERs remaining in most cases above £60,000 per QALY gained. As with oral topotecan, in terms of parameter inputs, the results appear to be most sensitive to variation in utility estimates applied in the model, variation in values of parameters in the survival functions (for overall survival and time to progression) and to the cost of outpatient attendance for the administration of chemotherapy. Time horizon for the model appears to have a very limited impact on the cost effectiveness estimates, as does varying the discount rates applied in the model.

Cost effectiveness of IV topotecan – probabilistic analysis

In a probabilistic sensitivity analysis, where the parameters of the survival models (both overall survival and time to progression) probabilities of adverse events, proportionate deterioration in health state utility values, cost of outpatient attendances and patient monitoring as well as costs of managing adverse events and palliative care were sampled probabilistically, IV topotecan is associated with increased QALYs (with a range from 0.10 to 0.27 QALYs, when TTP is modelled using data from the RCT by von Pawel and colleagues[58] and from 0.11 to 0.33 QALYs, when time to progression is modelled using data from the RCT by Eckardt and colleagues[56]) but also increased costs (from £10,091 to £14,701 and from £9,669 to £15,422, when time to progression is modelled using data from the RCTs by von Pawel and colleagues[58] and by Eckardt and colleagues[56] respectively) in all simulations, when compared with BSC alone (see Figure 7, which also shows 95% confidence

ellipses for time to progression is modelled using data from the RCT by von Pawel and colleagues[58] (dashed ellipse) and by Eckardt and colleagues[56] (solid ellipse)).

Figure 7 Cost effectiveness plane – incremental cost and incremental QALYs for IV topotecan compared with BSC, with 95% confidence ellipses



The distributions assigned to each variable included in the probabilistic sensitivity analysis and the parameters of the distribution are reported in Appendix 10. One thousand simulations were run for this analysis. The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis (see Table 45 for the base case analysis). Table 48 reports the mean costs and outcomes from the probabilistic analysis (including the 2.5th and 97.5th percentiles to give an indication of the range of the simulated values) and the ICER for IV topotecan plus BSC compared with BSC alone, based on the mean values generated in the probabilistic analysis.

Table 48 Costs and outcomes from probabilistic analysis for IV topotecan

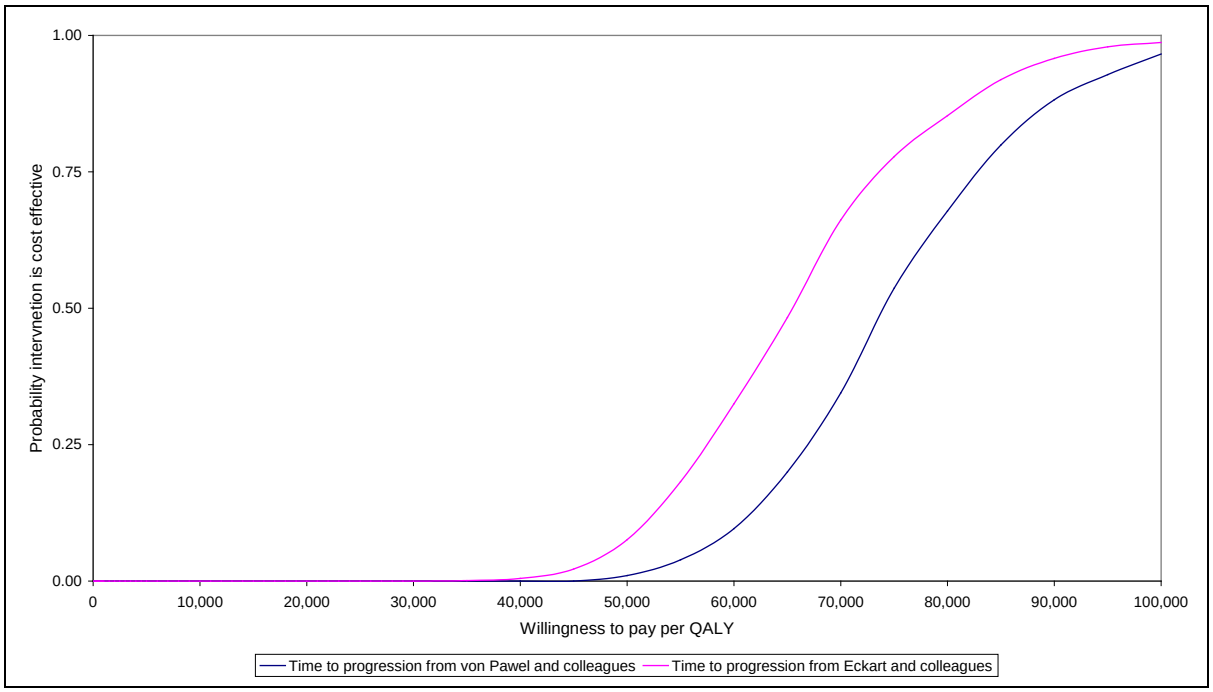
	Discounted costs			Discounted QALYs			
	Mean	2.5th Percentile	97.5th Percentile	Mean	2.5th Percentile	97.5th Percentile	ICER
BSC	4,829	2,305	8,652	0.2260	0.2054	0.2527	
IV topotecan and BSC	17,000[†] 17,387[‡]	14,089[†] 14,497[‡]	20,752[†] 21,203[‡]	0.3915[†] 0.4210[‡]	0.3438[†] 0.3615[‡]	0.4599[†] 0.4998[‡]	73,579[†] 64,418[‡]

[†] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by von Pawel and colleagues[58]
[‡] costs and outcomes calculated using time to progression for IV topotecan (relative to oral topotecan) from the RCT by Eckardt and colleagues[56]

The ICERs reported in Table 48, calculated using the difference in mean discounted costs and mean discounted QALYs shown in the table, are slightly lower than the mean of the ICERs calculated at each simulation (which were £75,325 and £66,444, when TTP is modelled using data from the RCTs by von Pawel and colleagues[58] and by Eckardt and colleagues,[56] respectively).

In addition to graphing the incremental cost and incremental QALYs for IV topotecan and BSC, cost effectiveness acceptability curves were derived for each analysis, representing the proportion of simulations where IV topotecan treatment is cost effective for a range of willingness to pay thresholds, up to £100,000 (see Figure 8). In this analysis IV topotecan plus BSC had a probability of being cost-effective of 0% at willingness to pay threshold of £20,000 and £30,000 per QALY and 1% at a willingness to pay threshold of £50,000 per QALY, when TTP is modelled using data from the RCT by von Pawel and colleagues.[58] When TTP is modelled using data from the RCT by Eckardt and colleagues,[56] the probability of being cost-effective remained at 0% at the lower willingness to pay thresholds but the probability of being cost-effective increased slightly (to 7.6%) at a willingness to pay threshold of £50,000 per QALY.

Figure 8 Cost effectiveness acceptability curve for IV topotecan and BSC



Summary of cost effectiveness

- A systematic search of the literature found no fully published economic evaluations of oral or IV topotecan as a treatment for patients with relapsed SCLC, for whom re-treatment with the first line regimen is not considered appropriate.
- A systematic search for published studies of QoL for patients with relapsed SCLC found no fully published studies other than the main RCT publication by O'Brien and colleagues.[57] There is very little detail on the methods used to analyse the utility data presented in the main trial report. The searches identified an additional publication, which is only available in abstract form,[64] which provided more details (including baseline utility scores for the trial arms). Further methodological detail was extracted from the CSR (submitted as an Appendix to the MS to NICE).
- The manufacturer submitted a dossier in support of oral topotecan, including an economic evaluation based on individual participant data from the RCT reported by O'Brien and colleagues.[57] This compares oral topotecan plus BSC with BSC alone. CAV was excluded from the manufacturer's analysis on the *a priori* basis that topotecan (oral or IV) would be unlikely to be a cost effective alternative, given its higher acquisition cost.
- Mean survival, in the manufacturer's model, was estimated directly from the survival durations for patients in the O'Brien and colleagues RCT.[57] Censored cases were assumed to have died on the day following censoring – the manufacturer conducted no sensitivity analysis in respect of this assumption.
- Health-related QoL was recorded using the EQ-5D, for up to 12 cycles (36 weeks), and valued using a general population tariff.[80] Missing values were imputed using data from the trial, using the mean utility score (across both trial arms) for missing values up to cycle 12. Where oral topotecan plus BSC patients survived with non-progressive disease beyond the 36-week data collection, the last observation was carried forward until disease progression occurred. Once these patients developed progressive disease, values for BSC patients were applied.
- Oral topotecan was costed at the observed total dose for each participant in the topotecan plus BSC arm of the RCT by O'Brien and colleagues[57] (with dosage rounded up to the nearest 0.25 mg). Chemotherapy administration was costed for the observed number of cycles for each patient, assuming one attendance per cycle to collect oral chemotherapy and assumed monitoring costs of £10 per cycle (using monitoring costs from a previous TAR,[69] which included topotecan, inflated to 2007/08 costs). Haematological adverse events were costed on the basis of the observed prescribing of GCSF and antibiotics, as well as blood products (RBC units and platelet units) delivered to patients in the RCT by O'Brien and colleagues,[57] with additional assumptions regarding costs of administration. All blood transfusions were assumed to be provided on a day case basis. Patients were assumed to be managed as day cases where drugs were administered intravenously, whereas patients receiving oral drugs were assumed to have their adverse events

managed in out-patients. Resource use for management of non-haematological adverse events was based on expert opinion and costed according to the proportion of non-haematological adverse events which were deemed to be treatment-related in the RCT by O'Brien and colleagues.[57] Resource use for monitoring patients following the cessation of treatment with topotecan, and prior to disease progression, was also based on expert opinion.

- In the manufacturer's base case, the QALY gain for the cohort of patients receiving oral topotecan and BSC was estimated at 0.211. The cost difference was £5,671, giving an ICER of £26,833 per QALY gained.
- Deterministic sensitivity analysis showed that the results were sensitive to methods of estimating QoL (methods of carrying forward utility scores when patients had missing data), drug administration cost (significantly higher costs if patient attend on five days of the cycle to receive chemotherapy) and adverse event costs (halving or doubling adverse event costs).
- In a bootstrap analysis, treatment with oral topotecan plus BSC was always associated with increased costs (incremental costs between £4,000 and £7,500) and with improved QALY outcomes (incremental QALYs between zero and approximately 0.6) in the majority (98%) of replications. Cost effectiveness acceptability curves reported in the MS estimate a probability of oral topotecan plus BSC being cost effective at 22% at a willingness to pay threshold of £20,000 per QALY and 60% at a willingness to pay threshold of £30,000 per QALY.
- Subgroup analyses showed that oral topotecan was more likely to be cost effective in patients whose time to progression from prior therapy was less than or equal to 60 days (ICER = £17,946 per QALY gained), in women (ICER = £11,708 per QALY gained) and in those patients without liver metastases (ICER = £21,291 per QALY gained). Treatment with oral topotecan plus BSC also appeared to be more cost effective for patients with a PS of 2 (ICER = £25,544 per QALY gained) as opposed to those with a PS of zero or 1 (ICER = £30,770 per QALY gained).
- We developed an independent model which adopted a survival model methodology, using the published Kaplan Meier estimates for overall survival and TTP data included in the MS. The model includes three states – relapsed SCLC, progressive disease and death.
- Utility values reported for participants in the RCT by O'Brien and colleagues[57] were used in the model. QoL data for the trial were reported as a rate of deterioration per three-month interval for participants in each arm in the trial, controlling for baseline utility. The reported reductions over three months were converted to daily utility reductions for use in our model and applied to the baseline utility values for participants in the RCT by O'Brien and colleagues.[57] The rate of deterioration reported for oral topotecan and BSC was used for participants prior to disease progression. To allow for poorer QoL in participants following disease progression the rate of deterioration reported for BSC alone was applied to oral topotecan patients who had experienced disease progression.

- Resource use associated with oral and IV topotecan were estimated from the included RCTs, the MS and using advice from clinical experts. Where insufficient detail was available (such as for palliative care), appropriate costs were taken from published sources. Drug costs were taken from the BNF.[79] Other unit costs were taken from NHS reference costs, Southampton University Hospitals Trust or published sources. Cost base for evaluation was 2007/08 financial year – where costs were taken from other cost years, these were adjusted using the HCHS Pay and Prices Index.
- The base case model has approximate lifetime horizon, with extrapolation of the survival functions up to five years in the base case. Alternative scenarios using a longer time horizon or limited to the maximum follow up in the RCT by O'Brien and colleagues[57] are reported in the deterministic sensitivity analysis to ascertain whether extrapolation using survival function introduces bias. Alternative forms of survival function were also investigated to asses the sensitivity of the cost effectiveness to structural assumptions.
- The gain in discounted life expectancy associated with the addition of oral topotecan to BSC, for patients with relapsed SCLC for whom re-treatment with the first line regimen is not considered appropriate, is 0.33 years in our model (approximately 16.9 weeks). The discounted QALY gain is 0.1830 QALYs. The incremental cost associated with the addition of oral topotecan to BSC is approximately £6,200, resulting in an ICER of £33,851 per QALY gained. Approximately 40% of the incremental cost of the addition of oral topotecan to BSC is associated with drug acquisition costs, while approximately 26% is accounted for by management of adverse events, the majority of which are non-haematological toxicities.
- The cost effectiveness results for oral topotecan plus BSC are generally robust to variation in the parameters included in the deterministic sensitivity analysis, with ICERs varying between £30,000 and £37,000 per QALY gained. Among the structural sensitivity analyses, the results are most sensitive to assumptions over the functional form for the survival functions. In terms of parameter inputs, the results are most sensitive to variation in utility estimates applied in the model, variation in values of parameters in the survival functions (for overall survival and time to progression) and the cost of outpatient attendance for the administration of oral chemotherapy.
- Probabilistic sensitivity analysis shows a 0% probability of oral topotecan plus BSC being cost effective, compared with BSC alone, at a willingness to pay threshold of £20,000. The equivalent figure for a willingness to pay threshold of £30,000 is 20%.
- The gain in discounted life expectancy associated with IV topotecan, for patients with relapsed SCLC for whom re-treatment with the first line regimen is not considered appropriate, in our model is 0.30 years (approximately 15.9 weeks) – approximately one week shorter than the base case analysis for oral topotecan. The discounted QALY gain is 0.1628 QALYs, when time to progression is modelled using data from the RCT by von Pawel and colleagues,[58] and 0.1910, when time to progression is modelled using data from the RCT by Eckardt and colleagues.[56] The

incremental cost associated with IV topotecan is approximately £12,000 (£12,060 and £12,514, when time to progression is modelled using data from the RCTs by von Pawel and colleagues,[58] and by Eckardt and colleagues,[56] respectively). For patients receiving treatment with IV topotecan, palliative care comprises 27% of total costs for this cohort, while the cost of active treatment with topotecan comprises 58% of total costs (35% drug costs and 23% for chemotherapy administration). The resulting cost for IV topotecan compared with BSC is between £74,074 and £65,507 per QALY gained, depending on assumptions regarding time to progression. Compared with oral topotecan, IV topotecan is strictly dominated (poorer outcomes at higher cost) when time to progression is modelled using data from the RCT by von Pawel and colleagues,[58] while the ICER is approximately £783,734 per QALY gained, when time to progression is modelled using data from the RCT by Eckardt and colleagues.[56]

- In a probabilistic sensitivity analysis IV topotecan had a zero probability of being cost effective, compared with BSC alone, at willingness to pay thresholds of £20,000 and £30,000 per QALY. For a willingness to pay threshold of £50,000 the equivalent figure was between 1% and 7.6%, depending on assumptions regarding time to progression.

5 IMPLICATIONS FOR OTHER PARTIES

Topotecan (oral or IV) appears to provide gains in life expectancy over BSC alone, for people with relapsed SCLC. Recent debates over the assessment of technologies for peoples with short life expectancies have argued that a persons' family and carers may place a high value on relatively small extensions of life expectancy. Such potential benefits need to be weighed against the impact of patients taking up treatment. Attendance at hospital on five consecutive days of each chemotherapy cycle, as would be the case with IV topotecan, may be an unacceptable burden for carers. While oral topotecan offers advantages in terms of frequency of attendance for chemotherapy administration, both forms of topotecan are associated with high incidences of grade 3 and grade 4 haematological toxicities which may have a substantial impact on patients' carers and families.

6 FACTORS RELEVANT TO NHS

Oral topotecan offers an active treatment option to peoples who were previously deemed only suitable for palliative care, with potential gains in life expectancy over BSC alone. Adoption of oral topotecan as an addition to BSC for people with relapsed SCLC, in whom re-treatment with first-line therapy is not considered appropriate, is likely to require some additional treatment capacity. People undergoing chemotherapy with oral topotecan will be required to attend outpatients once every three weeks to collect their medication, to undergo monitoring for treatment-related toxicity and assessment of disease progression as well as for general medical assessment. Additional capacity will be required for

management of serious adverse events, when they occur – the RCTs by O'Brien and colleagues[57], von Pawel and colleagues[58] and Eckardt and colleagues[56] suggest that grade 3 or 4 neutropenia will occur in 60-75% of people treated with oral topotecan, while 22-32% of people will experience grade 3 or 4 anaemia. Treatment with IV topotecan would have similar requirements, in terms of managing adverse events, but substantially higher requirements for chemotherapy administration – these are reflected in the treatment cost estimates developed for the independent model. As a consequence, IV topotecan appears unlikely to be a treatment of choice in normal NHS practice.

The SmPC for topotecan[74] makes clear that the supervision of people receiving treatment requires specialist knowledge and experience of the use of chemotherapeutic agents. On this basis it seems most likely that the active care component of management will be based in secondary care under management of clinical oncology, although this may also require coordination with primary care. Given the poor prognosis and relatively short life expectancy for those with relapsed SCLC, even those initially responding topotecan, management will also require coordination with palliative care services.

7 DISCUSSION

7.1 Statement of principal findings

Clinical effectiveness

The results from five RCTs were included in this systematic review. One RCT compared oral topotecan and BSC with BSC alone,[57] one compared IV topotecan with CAV combination therapy,[59] two compared oral topotecan with IV topotecan,[56,58] and one other IV topotecan with amrubicin.[63] In one of the included studies of oral versus IV topotecan[56] and the study comparing topotecan with amrubicin,[63] we could not ascertain with any certainty if the population in the trials exactly matched those of the marketing authorisation for topotecan; that is, participants were inappropriate for re-treatment with their first-line therapy. Therefore is not clear how generalisable to the likely eligible participants in a UK setting these studies are. In terms of demographic characteristics these studies, where reported, had similar population groups, participants were aged on average between 58 and 70 years, with a higher proportion of males and a higher proportion having had extensive SCLC. No studies provided details of the ethnicity of participants, although it may be assumed that a high proportion of the participants in the study by Inoue and colleagues[63] were of Asian origin. Assessment of methodological reporting and quality varied between the included studies. There was a risk of selection bias in three studies[56,58,63] and a risk of detection bias in all of the studies. Three studies were assessed as having an adequate intention-to-treat analysis however.[57-59]

The primary outcome measure in most studies was response rate. For this measure, the evidence showed that there was no difference between IV topotecan and IV CAV, and no difference between topotecan administered orally compared with IV. Response rate was seen to be better in those treated with amrubicin, although it is worth noting the lower dose of topotecan in this study. In the trial of oral topotecan compared to BSC, measurement of response rates were only appropriate in the treatment group and hence no comparison on this outcome can be made.

Other outcome measures included duration of response, time to progression, overall survival, symptoms, HR-QoL and toxicities/adverse events. The evidence showed that overall survival was better in those treated with oral topotecan compared to BSC (the primary outcome in this study). There were no differences in overall survival between IV topotecan and CAV therapy, IV topotecan and amrubicin, or oral topotecan compared with IV topotecan. Health related QoL was seen to favour topotecan in the oral topotecan versus BSC study, although results may need to be viewed critically due to a number of issues (noted above). In one of the studies comparing IV topotecan with oral topotecan there were reportedly no differences in QoL between study arms; however no data were reported. Where reported, it would appear that symptoms were favourable to topotecan therapy, although care is required as some scales may not have been validated measures. Toxicities were reported across treatment groups in all studies, except in the O'Brien and colleagues[57] study where no treatment was given to those in the BSC group. There were some grades of toxicities that showed higher rates in the topotecan arms of studies, however there were also some grades of toxicities that showed lower rates. This, together with the small sample sizes of the studies and the different comparators evaluated, mean that it is difficult to establish with any degree of certainty if topotecan is more or less toxic in those with SCLC than comparator interventions.

Cost effectiveness

Systematic searches identified no fully published economic evaluations of oral or IV topotecan for the treatment of relapsed SCLC, in patients who were not considered appropriate for re-treatment with their first line regimen and only limited information on QoL in patients with relapsed SCLC.

The manufacturer's submission included an economic evaluation which compared oral topotecan and BSC with BSC alone, based on individual participant data from the RCT reported by O'Brien and colleagues.[57] CAV was excluded from the manufacturer's analysis on the basis that topotecan (oral or IV) would be unlikely to be a cost effective alternative, given its higher acquisition cost. The QALY gain with oral topotecan and BSC, compared with BSC alone was estimated at 0.211, in the manufacturer's base case analysis. The cost difference was £5,671, giving an ICER of £26,833 per QALY gained. Deterministic sensitivity analysis showed that the results were sensitive to methods of estimating QoL, drug administration cost and adverse event costs, although the scenarios examined

for costs were extreme. Parametric cost effectiveness acceptability curves were used in the MS to estimate the probability of oral topotecan and BSC being cost effective, compared with BSC alone. The MS reported a probability of being cost effective of 22% at a willingness to pay threshold of £20,000 per QALY and 60% at a willingness to pay threshold of £30,000 per QALY.

Subgroup analyses undertaken with the manufacturer's model showed that oral topotecan was more likely to be cost effective in patients whose time to progression from prior therapy was less than or equal to 60 days (ICER = £17,946 per QALY gained), in women (ICER = £11,708 per QALY gained), and in those patients without liver metastases (ICER = £21,291 per QALY gained). Treatment with oral topotecan and BSC also appeared to be more cost effective for patients with a PS of 2 (ICER = £25,544 per QALY gained) as apposed to those with a PS of 0 or 1 (ICER = £30,770 per QALY gained).

The manufacturer's approach to estimating the cost effectiveness of oral topotecan appears generally reasonable. However, specific concerns were raised regarding the extent to which the within-trial QoL assessments captured the impact of adverse events for patients in the oral topotecan arm, the adequacy of approaches to imputing values where QoL data were missing and the lack of survival modelling for patients whose data were censored (although the proportion of censored cases is comparatively low).

We developed an independent model to assess the cost effectiveness of topotecan (oral or IV) compared with BSC, using survival analysis. The model consists of three states – relapsed SCLC, progressive disease and death and includes the utility estimates reported for patients in the RCT by O'Brien and colleagues.[57] In the base case we extrapolate survival up to five years.

Resource use associated with oral and IV topotecan was estimated from included RCTs, the MS, advice from clinical experts and published sources. Unit costs were taken from the BNF,[79] NHS Reference Costs and other published sources. Where published estimates were inadequate we used costs supplied by the Southampton University Hospitals Trust. The cost base for the evaluation was 2007/08 financial year.

The gain in discounted life expectancy associated with the addition of oral topotecan to BSC in our model is 0.33 years (approximately 16.9 weeks). The discounted QALY gain is 0.1830 QALYs. The incremental cost associated with the addition of oral topotecan to BSC is approximately £6,200, resulting in an ICER of £33,851 per QALY gained. The cost effectiveness results for oral topotecan and BSC are generally robust to variation in the parameters included in the deterministic sensitivity analysis. The results were most sensitive to assumptions over the form of survival functions adopted and variation in values of parameters in the survival functions, variation in utility estimates applied in

the model and the cost of outpatient attendance for the administration of oral chemotherapy. In a probabilistic sensitivity analysis we estimated a 0% probability of oral topotecan and BSC being cost effective, compared with BSC alone, at a willingness to pay threshold of £20,000 and a 20% probability at a willingness to pay threshold of £30,000 per QALY.

The gain in discounted life expectancy associated with IV topotecan, compared with BSC, in our model is 0.30 years (approximately 15.9 weeks) – approximately one week shorter than the base case analysis for oral topotecan. The discounted QALY gain is between 0.1628 QALYs and 0.1910 QALYs depending on assumptions regarding time to progression and the incremental cost is approximately £12,000. The resulting ICER for IV topotecan compared with BSC is between £74,074 and £65,507 per QALY gained, depending on assumptions regarding time to progression. Compared with oral topotecan, IV topotecan is strictly dominated or is associated with a very high ICER. A probabilistic sensitivity analysis for IV topotecan showed zero or very low probability of being cost effective, compared with BSC alone, at willingness to pay thresholds up to £50,000.

7.2 Strengths, limitations and uncertainties

This evidence synthesis has the following strengths:

- It is independent of any vested interest.
- It has been undertaken following the principles for conducting a systematic review. The methods were set out in a research protocol (Appendix 2), which defined the research question, inclusion criteria, quality criteria, data extraction process and methods to be employed at different stages of the review.
- An advisory group has informed the review from its initiation. The research protocol was informed by comments received from the advisory group and the advisory group has reviewed and commented on the final report.
- The review brings together the evidence for the clinical and cost-effectiveness of topotecan for SCLC. This evidence has been critically appraised and presented in a consistent and transparent manner.
- An economic model has been developed following recognised guidelines and systematic searches have been conducted to identify data for the economic model. The main results have been summarised and presented.

- Clinical evidence to populate the model has been extracted from reasonable quality RCTs included in the systematic review. The effect of treatment was assessed using appropriate measures (survival and quality adjusted survival) to model cost and outcome differences over the model time horizons. Additional relevant data on time to progression were included to take account of expected differences in QoL following disease progression.

In contrast, this review also has certain limitations and uncertainties which include:

- Where possible, the data included in the model are in the public domain. However additional data inputs such as TTP and adverse event data were extracted from the MS where these were not reported in sufficient detail in published sources. The model structure and data inputs are clearly presented in this report. This should facilitate replication and testing of our model assumptions.
- The resource use assumptions were developed with advice from clinical experts who advised on the development of this review. Our resource use assumptions and unit cost estimates were compared with those included in the MS to assess their comprehensiveness.
- There is substantial uncertainty over the QoL data included in the model. However these are key to assessing the cost effectiveness of chemotherapeutic interventions for cancer patients. Adverse events associated with highly toxic agents may entirely offset life expectancy or QoL gains for responding patients. To address this uncertainty we have tested the impact of assumptions regarding QoL in the model and attempted to identify which assumptions have greatest impact on the cost effectiveness results.
- The validity of applying the survival model approach has been examined by comparing the results from our model with those from the manufacturer's analysis. The survival model gives a higher estimate of mean survival than the manufacturer's model using individual participant data. This differences largely results from the assumption, in the manufacturer's model, that censored patients day on the day following censoring – this appears to have a disproportionately large effect for the oral topotecan and BSC cohort where one patient is censored after a relatively short period of follow-up, but also involves truncation of the maximum survival duration where up to 5% of patients in the oral topotecan and BSC arm of the trial were still alive.

7.3 Other relevant factors

A number of other issues that need to be taken into account when considering the results of the present review are noted below.

- Authors of trials were contacted to try to establish with certainty that the participant populations in the included trials met the marketing authorisation. Responses were received from three of

these authors (relating to four studies). However it remains uncertain whether the participant groups in these trials fully meet the licensed indication for topotecan.

- Only two RCTs reported any assessment of QoL issues, one of these reported no baseline data and reported only minimal information on participants included in the analysis and the other provided no data at all. It is therefore difficult to make any judgement about the impact of topotecan on a person's QoL.
- Dose escalations and reductions were permitted in the protocols of each of the included trials. However, full details of these changes are not always presented and it is therefore unknown if these dose changes would have a significant effect on the outcomes.
- The duration of many of the trials was unclear, but in many was likely to be less than 12 months, in part likely owing to the nature of SCLC which deteriorates rapidly. However, this does mean that long-term evidence on outcomes and adverse events are limited for those eligible for treatment with topotecan. This may mean that the impact of adverse events are underestimated.
- All but one of the included trials were multi-centre studies and it is unclear whether inter-centre variability is an issue within these trials, particularly on measurement of self-report outcomes such as QoL. In addition, all the studies included in this review included participants from countries other than the UK. It is difficult to determine how generalisable the results of the included studies are to the population within the UK.
- Four of the five included trials were sponsored evaluations by the manufacturer of topotecan.

8 CONCLUSIONS

Topotecan appears to improve survival in people with SCLC when compared to BSC alone, is as effective as CAV but less effective than amrubicin in terms of response rates, and shows comparable rates of treatment toxicities and adverse events with CAV and amrubicin based on the data available. Oral and IV topotecan were not seen to be different from one another on survival or measures of response.

In the cost effectiveness analysis topotecan (oral or IV) for patients with relapsed SCLC was associated with improved health outcomes compared with BSC. However these improved outcomes were achieved at increased cost. Costs for IV topotecan were substantially higher than for oral topotecan, while the health benefits are roughly equivalent (or possibly poorer). ICERs for IV topotecan, compared with BSC, were high and suggest it is unlikely to be a cost effective option for this group of patients. The ICER for oral topotecan compared with BSC was lower than for IV topotecan, but is at the upper extreme of the range conventionally regarded as cost effective from an

NHS decision making perspective. Sensitivity analyses suggest the exact value of the ICER is highly dependent on assumptions regarding QoL for patients with relapsed SCLC receiving oral topotecan.

8.1 Need for further research

- It is unlikely that any further RCTs of topotecan compared to BSC will be ethically acceptable, nor is it likely for there to be a need to undertake a further comparison with CAV therapy and there is little to be gained from undertaking further evidence of the effectiveness of IV versus oral topotecan. However, given the ongoing RCTs of topotecan versus amrubicin it would be desirable to update the current review when these report.
- Further research is required into the QoL of patients with relapsed SCLC, to identify the impact of disease progression on QoL. In the case of patients receiving active treatment further research is required on the impact of response (complete or partial response) and the impact of treatment-related adverse events on QoL.
- Further research on the impact of active treatment on resource use for palliative care would improve cost effectiveness models for topotecan. Data collection on resource use in the RCT by O'Brien and colleagues was not comprehensive. It is difficult to determine whether the lower proportion of patients receiving radiotherapy and palliative medication (in the topotecan and BSC arm) indicates a genuine reduction in palliative care interventions or a postponement until disease progression occurs.

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Appendix 1: Performance scales and response criteria in SCLC
A. Performance scales:
Eastern Cooperative Oncology Group (ECOG) performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead
From: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al*. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982;5:649-55.[18]	

Karnofsky performance index

Definition		
Able to carry on normal activity and to work	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated, although death is not imminent
	20	Very sick; hospitalization necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead
From Karnofsky DA, Abelmann WH, Craver LF, et al: The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer 1948;1:634–656.[19]		

B: Treatment response criteria

WHO criteria treatment response (summarised from[54])

Characteristic	Criteria
Measurability of lesions at baseline	1. Measurable, bi-dimensional (product of LD and greatest perpendicular diameter)[†] 2. Non-measurable/evaluable (e.g., lymphangitic pulmonary metastases, abdominal masses)
Objective response	1. Measurable disease (change in sum of products of LDs and greatest perpendicular diameters, no maximum number of lesions specified) CR: disappearance of all known disease, confirmed at ≥ 4 wk PR: ≥50% decrease from baseline, confirmed at ≥ 4 wk PD: ≥25% increase of one or more lesions, or appearance of new lesions NC: neither PR or PD criteria met 2. Non-measurable disease CR: disappearance of all known disease, confirmed at ≥ 4 wk PR: estimated decrease of ≥ 50%, confirmed at ≥ 4 wk PD: estimated increase of ≥ 25% in existent lesions or appearance of new lesions NC: neither PR or PD criteria met
Overall response	1. Best response recorded in measurable disease 2. NC in non-measurable lesions will reduce a CR in measurable lesions to an overall PR 3. NC in non-measurable lesions will not reduce a PR in measurable lesions
Duration of response	1. CR From: date CR criteria first met To: date PD first noted 2. Overall response From: date of treatment start To: date PD first noted 3. In patients who only achieve a PR, only the period of overall response should be recorded

LD = longest diameter, CR = complete response, PR = partial response, PD = progressive disease, NC = no change, SD = stable disease.

[†]Lesions that can only be measured unidimensionally are considered to be measurable (e.g., mediastinal adenopathy, malignant hepatomegaly).

RECIST criteria treatment response (summarised from[55])

Characteristic	Criteria
Measurability of lesions at baseline	1. Measurable, uni-dimensional (LD only, size with conventional techniques >20 mm; spiral computed tomography >10 mm) 2. Non-measurable: all other lesions, including small lesions. Evaluable is not recommended.
Objective response	1. Target lesions (change in sum of LDs, maximum of 5 per organ up to 10 total [more than one organ]) CR: disappearance of all target lesions, confirmed at ≥ 4 wk PR: ≥ 30% decrease from baseline, confirmed at 4 wk PD: ≥ 20% increase over smallest sum observed, or appearance of new lesions

	SD: neither PR or PD criteria met 2. Non-target lesions CR: disappearance of all target lesions and normalization of tumor markers, confirmed at ≥ 4 wk PD: unequivocal progression of non-target lesions, or appearance of new lesions Non-PD: persistence of one or more non-target lesions and/or tumour markers above normal limits
Overall response	1. Best response recorded in measurable disease from treatment start to disease progression or recurrence 2. Non-PD in non-target lesion(s) will reduce a CR in target lesion(s) to an overall PR 3. Non-PD in non-target lesion(s) will not reduce a PR in target lesion(s)
Duration of response	1. Overall CR From: date CR criteria first met To: date recurrent disease first noted 2. Overall response From: date CR or PR criteria first met (whichever status came first) To: date recurrent disease or PD first noted 3. SD From: date of treatment start To: date PD first noted

LD = longest diameter, CR = complete response, PR = partial response, PD = progressive disease, NC = no change, SD = stable disease.

Appendix 2: Methods from research protocol

1. Title of the project:
Topotecan for the second-line treatment of small cell lung cancer

2. Report methods for synthesis of evidence of clinical- and cost-effectiveness

A review of the evidence for clinical-effectiveness and cost-effectiveness will be undertaken systematically following the general principles outlined in CRD Report Number 4 (2nd Edition) 'Undertaking Systematic Reviews of Research on Effectiveness'.[53]

4.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical effectiveness studies reporting on comparisons between topotecan (oral or IV, but not combined) and BSC or other chemotherapy regimens (as described in section 5.2); (ii) studies reporting on the cost-effectiveness of topotecan and different second-line treatments, and the relative comparisons. The search strategy will also identify studies reporting resource use and costs, epidemiology and natural history.

The following electronic databases will be searched: The Cochrane library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); PreMedline In-Process & Other Non-Indexed Citations; Web of Knowledge Science Citation Index (SCI); Web of Knowledge ISI Proceedings; PsychInfo; Biosis; UKCRN Study Portfolio and Current Controlled Trials. Key cancer resources (such as the American Society of Clinical Oncology (ASCO), European CanCer Organisation (ECCO) etc.) and relevant cancer symposia will also be searched. The search strategy for Medline will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The MS to NICE will be assessed for any additional studies which meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished evidence.

Searches will be carried out from 1990 and will be limited to the English language. For the cost-effectiveness section, searches for other evidence to inform cost-effectiveness modelling will be conducted as required and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

4.2 Inclusion and exclusion criteria

4.2.1 Population

- Adults (≥18 years) with relapsed SCLC who responded to first-line treatment and for whom re-treatment with first-line therapy is not considered appropriate (due to contraindications, adverse effects).
- Patients may have limited stage disease or extensive stage disease.
- Response to initial treatment may be either complete response (CR) or partial response (PR).
- Patients who did not respond to first-line therapy (including patients whose tumours did not respond, or who progressed, during first-line treatment) will not be included.
- Studies with a mix of untreated and previously treated patients (or responders and non-responders), will not be included unless the groups are reported separately.

4.2.2 Intervention

- Intravenous topotecan
- Oral topotecan

(administered as second-line treatment)

- Studies with a focus on first-line treatment will not be included
- Effectiveness data for oral and intravenous topotecan will not be combined.

4.2.3 Comparators

- Intravenous and oral topotecan will be compared with each other
- Best supportive care (including radiotherapy)
- CAV (cyclophosphamide, doxorubicin, vincristine)
- Other chemotherapy regimens

4.2.4 Outcomes

Studies reporting one or more of the following outcomes will be included:

- time to disease progression
- progression-free survival
- response rate
- response duration
- overall survival
- symptom control
- health-related QoL (using a validated measure)

- cost-effectiveness (incremental cost per life year gained) or cost-utility (incremental cost per quality adjusted life year gained)

Adverse effects of treatments will be reported if available within trials that meet the other inclusion criteria.

4.2.5 Types of studies

- Fully published randomised controlled trials (RCTs) will be included. If no RCTs are found, controlled clinical trials and prospective cohort studies (with a concurrent control) will be eligible for inclusion
- Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations (cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses)
- Systematic reviews will be used as a source of references
- Case series, case studies, narrative reviews, editorials and opinions will not be included
- Non-English language studies will be excluded

4.3 Screening and data extraction process

4.3.1 Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by two reviewers. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by two reviewers and a final decision regarding inclusion will be agreed. At each stage, any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

4.3.2 Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 11.2). Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

4.4 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD (University of York) criteria.[53] Economic evaluations will be assessed using criteria recommended by Drummond and colleagues[66] (see Appendix 11.1.3), and/or the format

recommended and applied in the CRD NHS Economic Evaluation Database (using principles outlined in the NHS EED Handbook[81]). For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[68]). Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted.

4.5 Methods of data analysis/synthesis of clinical effectiveness data

Clinical effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using Review Manager (RevMan) software.

5. Methods of data analysis/synthesis of cost effectiveness data

5.1 Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations. Any economic evaluation included in sponsor submissions to NICE will be assessed using the same quality criteria as for published economic evaluations, but will be reported separately.

5.2 Economic Modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. The perspective will be that of the NHS and Personal Social Services. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per Quality Adjusted Life Year (QALY) gained, as well as the cost per life year gained if data permit. Both cost and outcomes will be discounted at 3.5%.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- The biological disease process (i.e. knowledge of the natural history of the disease);
- The main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events which are most important in determining patients' clinical outcomes, QoL and consumption of NHS or PSS resources.

For patients receiving topotecan, or comparator treatments, for relapsed SCLC following first-line treatment, time to disease progression will be a major factor in defining costs of second-line treatment and is also likely to be a significant determinant of QoL. Any improvements in overall survival or impacts on QoL that may be associated with changes in progression-free survival will need to be offset by consideration of the toxicity profile of alternative therapies. There is likely to be considerable uncertainty surrounding modes of treatment following disease progression on second-line treatment, which may have an influence on costs and QoL. Clinical guidance will be sought to define appropriate protocols for patient management following disease progression on second-line treatment.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or experts' clinical opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The simulated population will be defined on the basis of both the published evidence about the characteristics of UK population with SCLC relevant to the licensed indication for topotecan, and the populations for which good quality clinical effectiveness is available. The base case results will be presented for the population of UK patients undergoing second-line treatment of SCLC. The time horizon for our analysis will initially be governed by follow-up data available from included clinical trials - we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

5.2.1 Methods for estimating quality of life

The primary aim of treatment for SCLC is to palliate symptoms, prolong survival and maintain a good QoL with minimal adverse events from treatment. This assessment will aim to identify adverse effects of treatment that are likely to have a substantial impact on patients' QoL, and to include these in estimates of health state utility while on treatment. Where presented, QoL information as well as incidence of adverse events and side effects of treatment will be extracted from included RCTs. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. Ideally utility values will be taken from studies that have

been based on "public" (as opposed to patient or clinician) preferences elicited using a choice-based method (in accordance with NICE methodological guidance).[67]

5.2.2 Analysis of uncertainty

Analysis of uncertainty will focus on cost-utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

6. Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 12/12/08. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's guidance on presentation,[67] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Methods adopted, and incremental cost effectiveness ratios (ICERs) estimated from consultee models will be compared with published economic evaluations of topotecan included in the assessment report and with the results from the Assessment Group's analysis. Reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'academic in confidence' data or 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report.

Appendix 3: Sources of searches and search criteria

The following databases were searched for published studies and recently completed and ongoing research. All searches were limited to English language only. Searches were updated in February 2009.

- Cochrane Library – Cochrane Database of Systematic Reviews
- Cochrane Library – Central Register of Controlled Trials (Clinical Trials)
- Medline (OVID)
- PreMedline In-process & Other Non-indexed citations (OVID)
- Embase (OVID)
- Web of Knowledge Science Citation Index
- Web of Knowledge ISI Proceedings
- BIOSIS
- PsychInfo (Ebsco)
- Cinahl (Ebsco)
- DARE (NHS CRD)
- HTA (NHS CRD)
- NHS EED (NHS CRD)
- Health Technology Assessment (HTA) database;
- Current Controlled Trials
- Clinical Trials.gov
- Cancer Research UK trials
- NIHR-CRN Portfolio
- American Society of Clinical Oncology (ASCO)
- 12th World Lung Cancer Conference

Clinical Effectiveness searches

The following strategies were used to search MEDLINE (OVID) 1990-2008 and EMBASE (Ovid) 1990-2008. These were translated to search the other databases listed above.

MEDLINE(R)

1 Randomized Controlled Trials as Topic/ (56584)
2 randomized controlled trial.pt. (263468)
3 controlled clinical trial.pt. (79901)
4 Controlled Clinical Trial/ (79901)
5 placebos/ (28018)
6 random allocation/ (62530)
7 Double-Blind Method/ (99912)
8 Single-Blind Method/ (12433)
9 (random* adj2 allocat*).tw. (13703)
10 placebo*.tw. (113108)
11 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (96640)
12 crossover studies/ (22777)
13 (crossover* or (cross adj over*)).tw. (42546)
14 Research Design/ (54086)
15 ((random* or control*) adj5 (trial* or stud*)).tw. (332493)
16 clinical trials.sh. (0)
17 Clinical Trials as Topic/ (142719)
18 trial.ti. (76577)
19 randomly.ab. (124831)
20 (randomized or randomised).ab. (205326)

21 Drug Evaluation/ (41604)
22 Follow-Up Studies/ (377946)
23 prospective studies/ (251441)
24 Comparative Study/ (1425847)
25 Evaluation Studies as Topic/ (120471)
26 or/1-25 (2586344)
27 limit 26 to (english language and humans and yr="1990 - 2008") (1257730)
28 Topotecan/ (1346)
29 (topotecan or hycamtin).ti,ab. (1661)
30 or/28-29 (1860)
31 27 and 30 (561)
32 SCLC.ti,ab. (3693)
33 Carcinoma, Small Cell/ (15715)
34 Lung Neoplasms/ (123052)
35 33 and 34 (13271)
36 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (28814)
37 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (82293)
38 32 or 33 or 35 or 36 or 37 (88051)
39 31 and 38 (165)
40 from 39 keep 1-165 (165)

Embase (OVID)
1 Randomized Controlled Trial/ (161361)
2 RANDOMIZATION/ (26101)
3 PLACEBO/ (116829)
4 placebo*.tw. (106937)
5 random*.tw. (377424)
6 Randomization/ (26101)
7 Double Blind Procedure/ (70149)
8 single blind procedure/ (7734)
9 Crossover Procedure/ (20539)
10 (crossover* or (cross adj over*)).tw. (38438)
11 Controlled Clinical Trial/ (49917)
12 ((random* or control* or clinical*) adj5 (trial* or stud*)).tw. (500666)
13 (random adj5 allocat*).tw. (1308)
14 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (91281)
15 exp clinical trials/ (522756)
16 Prospective Study/ (76363)
17 Comparative Study/ (110563)
18 Evaluation/ (52829)
19 or/1-18 (1211004)
20 animal/ (18250)
21 human/ (6212410)
22 20 not (20 and 21) (14472)
23 19 not 22 (1210216)
24 limit 23 to (english language and yr="1990 - 2008") (977835)
25 *topotecan/ (1200)
26 hycamtin.ti,ab. (59)
27 topotecan.ti,ab. (1688)
28 or/25-27 (1856)
29 Lung Small Cell Cancer/ (9125)
30 SCLC.ti,ab. (3511)
31 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (27336)
32 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (68834)
33 or/29-32 (72839)

34 24 and 28 and 33 (257)
35 from 34 keep 1-257 (257)

Cost-effectiveness searches
The clinical effectiveness strategies above were combined with the following cost-effectiveness filters and run in MEDLINE (OVID) and EMBASE (OVID). The strategies were translated and run in the other databases noted above.

Medline (OVID)
1 exp economics/ (401622)
2 exp economics hospital/ (15764)
3 exp economics pharmaceutical/ (1958)
4 exp economics nursing/ (3849)
5 exp economics dental/ (3737)
6 exp economics medical/ (12120)
7 exp "Costs and Cost Analysis"/ (140560)
8 Cost Benefit Analysis/ (44369)
9 value of life/ (5057)
10 exp models economic/ (6055)
11 exp fees/ and charges/ (7457)
12 exp budgets/ (9937)
13 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw. (364284)
14 (cost$ or costly or costing$ or costed).tw. (215271)
15 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw. (55616)
16 (expenditure$ not energy).tw. (11749)
17 (value adj2 (money or monetary)).tw. (716)
18 budget$.tw. (11787)
19 (economic adj2 burden).tw. (1798)
20 "resource use".ti,ab. (2425)
21 or/1-20 (831568)
22 (news or letter or editorial or comment).pt. (1037052)
23 21 not 22 (769363)
24 topotecan/ (1348)
25 (topotecan or hycamtin).ti,ab. (1664)
26 24 or 25 (1863)
27 SCLC.ti,ab. (3694)
28 Carcinoma, Small Cell/ (15724)
29 Lung Neoplasms/ (123253)
30 28 and 29 (13275)
31 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (28891)
32 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (82493)
33 26 and (27 or 30 or 31 or 32) (377)
34 23 and 33 (12)
35 26 and 28 (171)
36 23 and 35 (5)
37 34 or 36 (12)
38 from 37 keep 1-12 **(12)**

EMBASE
1 cost$.ti. (38273)
2 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (45245)
3 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (14978)
4 (price$ or pricing$).ti,ab. (11266)

5 (financial or finance or finances or financed).ti,ab. (23140)
6 (fee or fees).ti,ab. (5171)
7 cost/ (20116)
8 cost minimization analysis/ (1383)
9 cost of illness/ (4659)
10 cost utility analysis/ (2350)
11 drug cost/ (33975)
12 health care cost/ (60374)
13 health economics/ (10179)
14 economic evaluation/ (4274)
15 economics/ (5647)
16 pharmacoeconomics/ (915)
17 budget/ (7640)
18 "resource use".ti,ab. (2184)
19 economic burden.ti,ab. (1743)
20 or/1-19 (207147)
21 (editorial or letter).pt. (638905)
22 20 not 21 (186062)
23 topotecan/ (4883)
24 (topotecan or hycamtin).ti,ab. (1695)
25 23 or 24 (4966)
26 Lung Small Cell Cancer/ (9151)
27 SCLC.ti,ab. (3517)
28 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (27408)
29 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (69004)
30 or/26-29 (73028)
31 22 and 25 and 30 (33)
32 from 31 keep 1-33 (33)

Quality of Life Searches
The following strategy was used to search MEDLINE (OVID) and EMBASE (OVID) and the strategies were translated and run in the other databases noted above.

MEDLINE
1 "Quality of Life"/ (70898)
2 (hql or hqol or "h qol" or hrqol or "hr qol").ti,ab. (3046)
3 ("hye" or "hyes").ti,ab. (47)
4 (euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab. (1330)
5 Quality-Adjusted Life Year/ (3593)
6 "quality adjusted life".ti,ab. (2709)
7 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (2200)
8 "disability adjusted life".ti,ab. (475)
9 "quality of wellbeing".ti,ab. (1)
10 "quality of well being".ti,ab. (221)
11 daly$.ti,ab. (552)
12 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (7995)
13 health$ year$ equivalent$.tw. (31)
14 disutil*.ti,ab. (87)
15 "Value of Life"/ (5057)
16 rosser.ti,ab. (63)
17 willingness to pay.tw. (1010)
18 standard gamble$.tw. (493)
19 time trade off.tw. (414)

20 time tradeoff.tw. (160)
21 health utilit*.ab. (493)
22 or/1-21 (83056)
23 topotecan/ (1348)
24 (topotecan or hycamtin).ti,ab. (58)
25 23 or 24 (1358)
26 SCLC.ti,ab. (3694)
27 "small cell lung cancer".ti,ab. (19336)
28 Carcinoma, Small Cell/ (15724)
29 Lung Neoplasms/ (123253)
30 28 and 29 (13275)
31 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (28891)
32 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (82493)
33 25 and (26 or 27 or 30 or 31 or 32) (271)
34 22 and 33 (10)
35 (quality adj5 topotecan).ti,ab. (9)
36 (qol adj5 topotecan).ti,ab. (3)
37 (quality adj5 hycamtin).ti,ab. (1)
38 (qol adj5 hycamtin).ti,ab. (0)
39 or/35-37 (12)
40 22 and 39 (9)
41 34 or 40 (16)
42 from 41 keep 1-16 (16)
43 Survival Analysis/ (69669)
44 "symptom palliation".mp. (141)
45 43 or 44 (69782)
46 33 and 45 (39)
47 46 not 42 (36)
48 from 47 keep 1-36 (36)
49 from 41 keep 1-16 (16)

EMBASE
1 exp quality of life/ (94730)
2 quality adjusted life year/ (3820)
3 quality adjusted life.ti,ab. (2591)
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (2096)
5 disability adjusted life.ti,ab. (428)
6 daly*.ti,ab. (465)
7 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (7682)
8 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (845)
9 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (953)
10 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (11)
11 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (193)
12 (euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab. (1315)
13 (hql or hqol or "h qol" or hrqol or "hr qol").ti,ab. (2915)
14 ("hye" or "hyes").ti,ab. (28)
15 health* year* equivalent*.ti,ab. (24)
16 ((health or cost) adj5 util*).ti,ab. (10006)
17 (hui or hui1 or hui2 or hui3).ti,ab. (399)

18 disutil*.ti,ab. (88)
19 rosser.ti,ab. (51)
20 quality of well being.ti,ab. (197)
21 quality of wellbeing.ti,ab. (5)
22 qwb.ti,ab. (114)
23 willingness to pay.ti,ab. (972)
24 standard gamble*.ti,ab. (447)
25 time trade off.ti,ab. (392)
26 time tradeoff.ti,ab. (144)
27 tto.ti,ab. (307)
28 (index adj2 well being).mp. (277)
29 (quality adj2 well being).mp. (511)
30 (health adj3 util* adj ind*).mp. (372)
31 ((multiattribute* or multi attribute) adj3 (health ind* or theor* or health state* or util* or analys*)).mp. (152)
32 quality adjusted life year*.mp. (4639)
33 (EORTC adj2 "LC-13").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2)
34 FACT-L.mp. (37)
35 LCSS.mp. (35)
36 or/1-35 (108127)
37 topotecan/ (4904)
38 topotecan.mp. (4988)
39 hycamtin.mp. (447)
40 or/37-39 (4988)
41 Lung Small Cell Cancer/ (9172)
42 SCLC.ti,ab. (3524)
43 (small cell* adj3 (cancer* or carcinoma*)).ti,ab. (27478)
44 (lung* adj3 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)).ti,ab. (69221)
45 or/41-44 (73251)
46 36 and 40 and 45 (94)
47 (letter or editorial or comment).pt. (641036)
48 46 not 47 (90)

Epidemiology searches

The following strategies were used to search MEDLINE (OVID) and EMBASE (OVID)

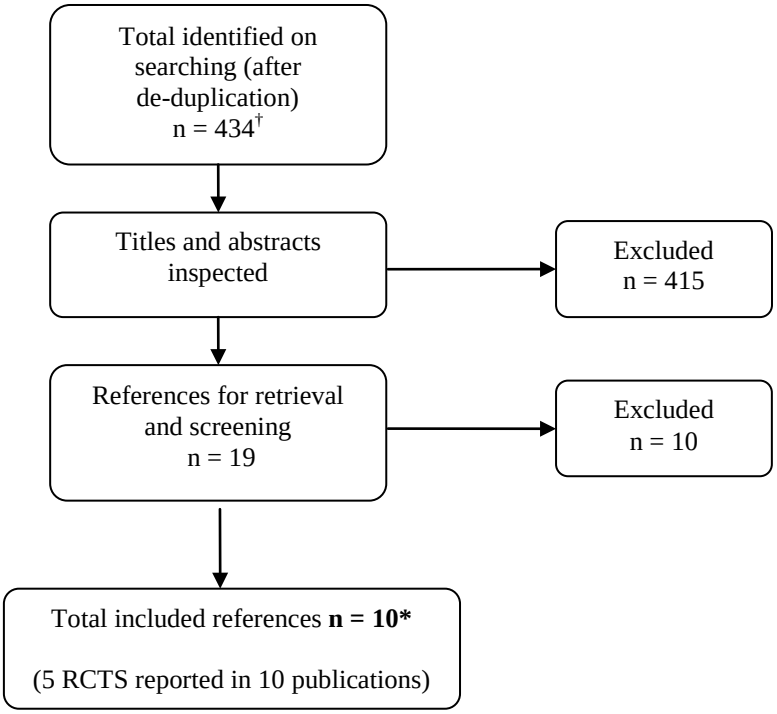
1 *carcinoma small cell/ep (161)
2 *lung neoplasms/ (94669)
3 1 and 2 (124)
4 *lung small cell cancer/ep (162)
5 (("small cell lung cancer" or SCLC) adj3 (incidence or prevalence or epidemiolog* or mortality or morbidity or aetiology or etiology)).ti,ab. (128)
6 "non small cell lung cancer".ti. (18884)
7 5 not 6 (80)
8 5 not 7 (48)
9 *carcinoma small cell/et (247)
10 *lung cancer/et (7046)
11 9 and 10 (74)
12 (SCLC and aetiology).ti,ab. (9)
13 (SCLC and etiolog*).ti,ab. (35)
14 ("small cell lung cancer" and etiolog*).ti. (1)
15 ("small cell lung cancer" and aetiolog*).ti. (0)
16 lung cancer trend*.ti,ab. (55)
17 lung cancer pattern*.ti,ab. (24)

18 lung cancer epidemiolog*.ti,ab. (80)
19 3 or 4 or 7 or 11 or 12 or 13 or 14 or 16 or 17 or 18 (624)
20 limit 19 to english language (529)
21 NSCLC.ti. (1555)
22 "non small cell lung cancer".ti. (18884)
23 21 or 22 (19767)
24 20 not 23 (516)
25 remove duplicates from 24 (395)
26 from 25 keep 1-251 (251) – note this is the medline set downloaded separately for import purposes)
27 from 25 keep 252-395 - note this is the embase record set downloaded separately for import purposes)

Additional Searching

Bibliographies: all references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Figure 9 Flow chart of identification of studies for inclusion in the review



†Includes total number of studies identified in searches of ASCO, 12th world lung cancer conference and updated search in addition to main search; *one identified ASCO abstract subsequently published as a full publication.

Appendix 4: SHTAC peer review of clinical effectiveness in manufacturer's submission of topotecan for SCLC.

Other consultee submissions checked and nothing to add.

Comprehensiveness of ascertainment of published studies
Clinical effectiveness:
- databases and dates of searches were specified in an Appendix 'full systematic review' (no full check of this was made)
- search strategies in Annex of Appendix (not fully checked)
- enough detail provided to be reproducible
- searched for ongoing studies
- no direct searching of conference proceedings, although Google'd

Cost effectiveness:
- search terms specified (although minimal)
- only searched NHS EED
- however, unlikely that anything was missed

Searches identified:
- 4 clinical trials (oral topotecan Vs BSC; IV topotecan Vs CAV; Oral topotecan Vs IV topotecan X 2).
- did not identify our fifth study (IV Vs Amrubicin) – possibly as no conferences were directly searched and owing to date of their searches.
- no cost effectiveness studies identified
- also searched for indirect comparisons but found no studies of value

Clinical Analysis:
- evidence reported is similar to ours with the exception of the **amrubicin study**, except they do not appear to report the **new QOL data** from the O'Brien study.
- their conclusions are similar to ours
- they indirectly compared oral Vs CAV (no real rationale given but see below). They observed the survival data and statistically compared the overall response rate data only.
- adverse event reporting is similar to ours. They undertook a meta-analysis of some data (not checked to see if data is consistent with a M/A).

Interpretation:
- their interpretation of the clinical data matches their analyses

Questions:
The clinical effectiveness review ran an indirect comparison of oral topotecan vs CAV. Although no justification for this was given directly it is assumed this is because CAV is the most likely comparator in this population and that although IV treatment has been compared to CAV in a trial, a proportion of patients would prefer oral topotecan. In the economic evaluation however, CAV is not considered as it is reported that this would not be a cost-effective option due to the higher cost of topotecan. So, although on paper the comparator would be CAV, assume the manufacturer's view is that the comparator should be those who are ineligible for CAV (this population would be a part of those in the O'Brien trial as they were 'not appropriate' for further IV treatment). In addition, the population in the CAV trial were excluded if they were ineligible for CAV so will not be those 'eligible' for topotecan in this sense.

Appendix 5: Quality assessment criteria

Quality criteria for assessment of experimental studies[53]

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

Some instructions for using a checklist for RCTs

Quality item	Coding	Explanation
1. Was the assignment to the treatment groups really random?		
Random sequence generation	Adequate Partial Inadequate Unknown	Adequate: random numbers table or computer and central office or coded packages Partial: (sealed) envelopes without further description or serially numbered opaque, sealed envelopes Inadequate: alternation, case record number, birth date, or similar procedures Unknown: just the term 'randomised' or 'randomly allocated' etc.
2. Was the treatment allocation concealed?		
Concealment of randomisation The person(s) who decide on eligibility should not be able to know or be able to predict with reasonable accuracy to which treatment group a patient will be allocated. In trials that use good placebos this should normally be the case, however different modes or timing of drug administration in combination with the use of small block sizes of known size may present opportunities for clinicians who are also involved in the inclusion procedure to make accurate guesses and selectively exclude eligible patients in the light of their most likely treatment allocation; in centres with very low inclusion frequencies combined with very brief follow-up times this my also present a potential problem because the outcome of the previous patient may serve as a predictor of the next likely allocation.	Adequate Inadequate Unknown	Adequate: when a paper convinces you that allocation cannot be predicted (separate persons, placebo really indistinguishable, clever use of block sizes (large or variable). Adequate approaches might include centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer based system with a randomisation sequence that is not readable until allocation, and other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate: this option is often difficult. You have to visualise the procedure and think how people might be able to circumvent it. Inadequate approaches might include use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) and any other measures that cannot prevent foreknowledge of group allocation. Unknown: no details in text. Disagreements or lack of clarity should be discussed in the review team.
3. Were the groups similar at baseline regarding the prognostic factors?		
Baseline characteristics Main aim is to enable the reviewer to see which patients were actually recruited. It enables one to get a rough idea on prognostic comparability. A real check on comparability requires multivariable stratification (seldom shown).	Reported Unknown	Consult the list of prognostic factors or baseline characteristics (not included in this appendix) Reviewer decides
4. Were the eligibility criteria specified?		

Prestratification Consult the list of prognostic factors or baseline characteristics (not included in this appendix).	Adequate Partial Inadequate Unknown	Single centre study Adequate: prestratification on at least one factor from the list or no prestratification if the number of patients exceeds a prespecified number. Partial: leave judgement to reviewer Inadequate: stratification on a factor(s) not on our list or no stratification whereas the number of patients is less than the prespecified number Unknown: no details in text and no way to deduce the procedure from the tables. Multicentre study Adequate: must prestratify on centre. Within each centre the criteria for single centre studies also apply Partial: impossible option Inadequate: no prestratification on centre or violating the criteria for single centre studies (see above) Unknown: no details in text and no way to deduce the procedure from the tables.
5. Were outcome assessors blinded to the treatment allocation?		
Blinding of assessors The assessor may be the patient (self report), the clinician (clinical scale, blood pressure, ..) or, ideally, a third person or a panel. Very important in judgement of cause of death but unimportant in judgement of death.	Adequate Inadequate Unknown	Adequate: independent person or panel or (self) assessments in watertight double-blind conditions Inadequate: clinician is assessor in trial on drugs with clear side effects or a different influence on lab results, ECGs etc Unknown: no statements on procedures and not deducible
6. Was the care provider blinded?		
Blinding of care givers Look out for good placebos (see, hear, taste, feel, smell), tricky unmasking side effects accounting for the subjectivity of the outcome measurements and the accessibility of co-interventions by the caregivers.	Adequate Partial Inadequate Unknown	Adequate: placebo described as ‘indistinguishable’ and procedures watertight (use your imagination with the 'cheat' in mind; e.g. statement that sensitive/ unmasking lab results were kept separate from ward personnel) Partial: just ‘double blind’ in text and no further description of procedures or nature of the placebo Inadequate: wrong placebo (e.g. fructose in trial on ascorbic acid) Unknown: no details in text
Co-interventions		
Register when they may have an impact on any of the outcome phenomena. Consult the list of cointerventions (not included in this appendix).	Adequate Partial Inadequate Unknown	Adequate: percentages of all relevant interventions in all groups Partial: one or more interventions omitted or omission of percentages in each group Inadequate: not deducible Unknown: no statements
7. Was the patient blinded?		
Blinding of patients This item is hard to define. Just the statement ‘double blind’ in the paper is really insufficient if the procedure to accomplish this is not described or reasonably deducible by the reviewer. Good placebos (see, hear, taste, feel, smell), tricky unmasking side effects accounting for the subjectivity of the outcome measurements and the accessibility of co-interventions by the patient are required.	Adequate Partial Inadequate Unknown	Adequate: placebo described as ‘indistinguishable’ and procedures watertight Partial: just ‘double blind’ in text and no further description of procedures or nature of the placebo Inadequate: wrong placebo Unknown: no details in text
Compliance Dosing errors and timing errors.	Adequate Partial	Adequate: Medication Event Monitoring System (MEMS or eDEM)

	Inadequate Unknown	Partial: blood samples, urine samples (use of indicator substances) Inadequate: pill count or self report Unknown: not mentioned
Check on blinding Questionnaire for patients, care givers, assessors and analysis of the results; the (early) timing is critical because the treatment effect may be the cause of unblinding, in which case it may be used as an outcome measure.	Reported Unknown	Reviewer decides
8. Were the point estimates and measure of variability presented for the primary outcome measure?		
Results for the primary outcome measure	Adequate Partial Inadequate Unknown	Adequate: mean outcome in each group together with mean difference and its standard error (SE) or standard deviation (SD) or any CI around it or the possibility to calculate those from the paper. Survival curve with logrank test and patient numbers at later time points Partial: partially reported Inadequate: no SE or SD, or SD without N (SE = SD/N) Unknown: very unlikely
9. Did the analysis include an intention to treat analysis?		
Intention-to-treat analysis (ITT) Early drop-out can make this very difficult. Strictest requirement is sensitivity analysis including early drop-outs.	Adequate Inadequate	Reviewers should not just look for the term ITT but assure themselves that the calculations were according to the ITT principle.
Dealing with missing values The percentage missing values on potential confounders and outcome measurements (seldom given) is a rough estimate of a trial's quality. One can carry them forward, perform sensitivity analysis assuming the worst and best case scenarios, use statistical imputation techniques, etc. Note that the default option (deletion) assumes that the value is randomly missing, which seems seldom justified.	Adequate Partial Inadequate Unknown	Adequate: Percentage of missing values and distribution over the groups and procedure of handling this stated Partial: some statement on numbers or percentages Inadequate: wrong procedure (a matter of great debate) Unknown: no mentioning at all of missing and not deducible from tables
Loss to follow-up This item examines both numbers and reasons; typically an item that needs checking in the methods section and the marginal totals in the tables. Note that it may differ for different outcome phenomena or time points. Some reasons may be reasons given by the patient when asked and may not be the true reason. There is no satisfactory solution for this.	Adequate Partial Inadequate Unknown	Adequate: number randomised must be stated. Number(s) lost to follow-up (dropped out) stated or deducible (from tables) for each group and reasons summarised for each group. Partial: numbers, but not the reasons (or vice versa) Inadequate: numbers randomised not stated or not specified for each group Unknown: no details in text

Appendix 6: Data extraction forms

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #268 (& earlier abstract Eckardt #720) Author: Eckardt *et al.* Year: 2007 Country: N. America, Europe, S.E. Asia & Australia Study design: Open-label RCT Number of centres: 83 Funding: GSK	<u>Group A:</u> Oral topotecan* Dose: 2.3 mg/m^2/d Duration: on days 1-5 every 21 days <u>Group B:</u> I.V. topotecan Dose: 1.5 mg/m^2/d, (30 min infusion) Duration: on days 1-5 every 21 days Pts with complete response (CR) or partial response (PR) continued treatment until disease progression or for 2 courses beyond best response. Those with stable disease were recommended to receive at least 4 courses. Dose escalation if no toxicity >grade 2 during course 1. Oral dose increased in increments of 0.4 mg/m^2 to a max of 3.1 mg/m^2/d. IV dose increased by 0.25 mg/m^2 to a max of 2.0 mg/m^2/d. Dose reduction if pts had prolonged or severe neutropenia or severe thrombocytopenia. Min doses were 1.5 mg/m^2/d for oral and 1.0 mg/m^2/d for IV; study withdrawal if delays of >2 wks at these doses. *Oral capsules contained topotecan hydrochloride equivalent to 0.25mg or 1.00mg of the anyhydrous free base.	*Number of Participants*: 309 Randomly assigned: Oral = 155, IV = 154 Received treatment: Oral = 153, IV = 151 *Sample attrition/dropout*: total = 57 (18%), oral = 31/155 (20%), IV = 26/154 (17%). Received no treatment: oral = 2, IV = 3; protocol violation: oral = 2, IV = 0; withdrew for AEs: oral = 19 (12%), IV = 19 (13%); withdrew for other reasons: oral = 6, IV = 3; lost to follow-up: oral = 1, IV = 1. *Sample crossovers*: n/a *Inclusion criteria*: pts with limited- or extensive-stage relapsed SCLC who had CR or PR to 1st line therapy with disease recurrence after ≥90 days; ≥18yrs, only 1 prior chemo regimen, bidimensionally measurable disease (according to WHO criteria), an Eastern Cooperative Oncology Group performance status ≤2, WBC count ≥3,500/µL, neutrophils ≥ 1,500µL, platelets ≥100,000µL, Hb ≥ 9.0 g/dL, serum creatinine ≤1.5 mg/dL, bilirubin ≤2.0 mg/dL; alkaline phosphatase, AST, and ALT≤2 x the upper limit of normal (ULN) or ≤5 x ULN with liver metastases; pts with CNS metastases if they were asymptomatic without corticosteroids; prior surgery was allowed if ≥4 wks had passed, as was immunotherapy (≥3 mths) and radiotherapy (≥24 hrs). *Exclusion criteria*: concurrent chemotherapy, immunotherapy, or radiotherapy; concurrent radiation for palliation of bone or brain lesions unless discussed with the medical monitor. *Characteristics of participants*: Gender (M/F), n (%): 194/110 (64%/36%); oral 98/55 (64.1% / 35.9%), IV 96/55 (63.6% / 36.4%) Age (yrs), mean (range): oral 62.5 (41-82), IV 62.0 (35-82) Disease stage, n (%): Limited: oral 51 (33.3%), IV 45 (29.8%) Extensive: oral 102 (66.7%), IV 106 (70.2%) Performance status, n (%): 0: oral 48 (31.4%), IV 35 (23.2%) 1: oral 85 (55.6%), IV 98 (64.9%) 2: oral 20 (13.1%), IV 18 (11.9%) Max lesion diameter (cm), n (%):[a]	Primary outcomes: Response rate Secondary outcomes:[d] • Time to response • Response duration • Time to progression • Overall survival • Toxicities • HRQoL Methods of assessing outcomes: Responses were verified by a central radiologist blinded to study treatment. Lesions were assessed at the end of each course (if evaluated by photography or physical examination) or at the end of alternate courses (if evaluated by CT or MRI x-ray, or ultrasound). The same method of evaluation was used throughout the study. HRQoL was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) 44-item self-reported instrument, validated & including 4 generic dimensions and a sub-scale specific to lung cancer. Trial Outcome Index (TOI) also derived from a sub-group of data. No details of scoring methods. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria. Length of follow-up: Pts received a median of 4 courses (i.e. 12 wks); at least 40% of pts in each group received treatment beyond course 4.

	Other interventions used: none	<2: oral 1 (0.7%), IV 2 (1.3%) 2 to <5: oral 88 (57.5%), IV 79 (52.3%) 5 to 10: oral 54 (35.3%), IV 65 (43.0%) >10: oral 6 (3.9%), IV 5 (3.3%) Previous treatment: platinum-based and anthracycline-based combination regimens.[b] Response, n (%): not reported Response type, n (%): not reported Duration of response to 1st-line chemotherapy, n (%):[c] < 3 mths: oral 15 (9.8%), IV 13 (8.6%) 3-6 mths: oral 50 (32.7%), IV 54 (35.8%) > 6 mths: oral 84 (54.9%), IV 83 (55.0%) Liver metastases, n (%): Present: oral 44 (28.8%), IV 43 (28.5%) Absent: oral 109 (71.2%), IV 108 (71.5%)	

[a]Data missing for 4 pts in the oral group.
[b]Prior chemotherapy included cisplatin or carboplatin + etoposide; vincristine + cisplatin or carboplatin + etoposide; or cyclophosphamide + epirubicin + cisplatin or carboplatin + etoposide. 129 patients (84.3%) in the oral group and 125 patients (82.8%) in the IV group had received prior combination chemotherapy that included platinum (cisplatin or carboplatin). Approx 10% of pts in both treatment groups had a treatment-free interval of < 90 days at study entry.
[c]Data missing for 4 pts in the oral group and 1 pt in the IV group.
[d]Time to response - from 1st topotecan dose to 1st documented CR or PR in pts who achieved a response; duration of response -from when response was 1st documented to disease progression; time to progression - from 1st topotecan dose to progression; survival - from 1st dose until death.

RESULTS

Outcomes	**Oral topotecan (n = 153)**	**IV topotecan (n = 151)**	**Difference**
Overall survival time (wks), median (range) 95% CI Survival rate: at year 1 at year 2	n=153 33.0 (0.3 to 185.3) 29.1 to 42.4 33% 12%	n=151 35.0 (0.7 to 205.3) 31.0 to 37.4 29% 7%	Hazard ratio[e] = 0.98 (95% CI 0.77 to 1.25) (NS)
[e]Cox proportional hazards regression. • For overall survival, data was censored for 13.7% and 10.6% of pts in oral and IV groups respectively.			
Time to progression (wks), median (range) 95% CI	n=153 11.9 (0.3 to 149.0)[f] 9.7 to 14.1	n=151 14.6 (0.7 to 177.9)[f] 13.3 to 18.9	
[f]includes censored events.			
Progression-free survival	not reported	not reported	
Overall response rate, n (%) -complete response -partial response	28 (18.3%) 95% CI 12.2% to 24.4% 2 (1.3%) 26 (17.0%)	33 (21.9%) 95% CI 15.3% to 28.5% 0 33 (21.9%)	Difference (oral – IV) -3.6% (95% CI -12.6% to 5.5%)
• Of 43 pts with baseline brain or leptomeningeal metastases, 1pt (IV arm) experienced a partial response.			
Time to response (wks), median (range)	n=28 6.1 (4.4 to 17.7)	n=33 6.1 (2.1 to 13.9)	
Response duration (wks), median (range)	n=28 18.3 (9.0 to 65.4)	n=33 25.4 (8.4 to 132.1)[f]	
[f]includes censored events.			
Non-responders, n (%)			

-stable disease	27 (17.6%)	35 (23.2%)	
-progressive disease	78 (51.0%)	65 (43.0%)	
-not assessable	20 (13.1%)	18 (11.9%)	

[g]states 32 pts not assessable for response due to death, withdrawal or completion of treatment after 1 or 2 courses. These pts received insufficient treatment to assign a response, but n=38 were classed as not assessable (table 2).

HRQoL	No data reported		

- HRQoL questionnaire response was 75% and 78% for oral and IV groups respectively after 2 courses of therapy. Rates at which pts failed to complete QoL assessment at 1 or more courses were similar between groups (no data provided).
- Least squares estimates for mean change from baseline indicated no statistical difference between treatment groups for subscale dimension scores and lung cancer scale (LSC), TOI and FACT-L total scores. Only a small decline in HRQoL was noted for each treatment group compared with declines that may be expected in an untreated lung cancer population (i.e. best supportive care). Mean change from baseline to last course also showed no statistical differences between groups (no data provided).

	Oral topotecan		**IV topotecan**		**Difference**
Adverse Effects, n (%)[h]	Grade 3	Grade 4	Grade 3	Grade 4	Not tested
leukopenia	64 (42.7)	34 (22.7)	74 (49.3)	39 (26.0)	
neutropenia	39 (26.2)	70 (47.0)	35 (23.6)	95 (64.2)	
thrombocytopenia	30 (20.0)	43 (28.7)	38 (25.3)	27 (18.0)	
anaemia	26 (17.3)	8 (5.3)	42 (28.0)	4 (2.7)	
Non-haematologic AE, (n) %:	Grade 3	Grade 4	Grade 3	Grade 4	Not tested
	11 (7.2)	1 (0.7)	3 (2.0)	1 (0.7)	
diarrhoea	10 (6.5)	0	10 (6.6)	2 (1.3)	
fatigue	9 (5.9)	3 (2.0)	10 (6.6)	5 (3.3)	
dyspnea	8 (5.2)	0	3 (2.0)	1 (0.7)	
anorexia	6 (3.9)	0	3 (2.0)	1 (0.7)	
nausea	4 (2.6)	3 (2.0)	7 (4.6)	3 (2.0)	
asthenia	3 (2.0)	3 (2.0)	4 (2.6)	6 (4.0)	
fever					
Received systemic antibiotic (%)	41%		56%		
	14%		23%		
Received IV antibiotic (%)	6		4		
Death, n[j]					

[h]occurring with a frequency of ≥10% in either treatment group; [j]died as a result of hematologic toxicity, septic shock related to topotecan treatment or of other causes possibly related to topotecan treatment.

- Granulocyte colony-stimulating factor was administered to 25% (oral) vs 16% (IV) of pts, although the proportion of treatment courses was similar in both groups (9% vs 7% respectively). With the protocol-specified dose adjustments, there was no evidence of cumulative toxicity.
- At time of analysis, 267 pts had died of which 250 were due to disease progression.
- Fever and/or infection (≥grade 2) associated with grade 4 neutropenia, together with sepsis, occurred in 5% of courses in both groups.

Additional comments:

- Data collected during post-study monitoring showed that similar proportions of pts in each group had received 3rd-line chemotherapy – 33% in oral group and 35% in IV group.
- Median dose intensity was 3.74 mg/m^2 (oral) and 2.31 mg/m^2 (IV), ratio = 1.61 which reflects the difference in oral and IV doses (ratio = 1.53). Dose reductions were made for 31% (oral) and 35% (IV) of pts primarily at the end of course 1 due to haematologic toxicity. 36% (oral) and 19% (IV) had a dose escalation.

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: Randomised 1:1. No details on randomisation method. Groups were stratified according to duration of response to first-line therapy (progression ≤6 months or >6 months), gender and presence or absence of liver metastases.
- Blinding: open-label study. An independent central radiologist who was blinded to study treatment verified all responses, though it is not clear whether this was the case for all outcome measures.
- Comparability of treatment groups: states that demographics and baseline characteristics were well matched between groups – not supported statistically, but groups do appear comparable (based on those who received at least 1 course of treatment).
- Method of data analysis: ITT population included all pts who received treatment (not all randomised pts). Time to event

data were summarised using Kaplan-Meier survival methods. A hazard ratio for treatment in the presence of covariates (i.e. duration of prior response, sex and liver metastases) using Cox's proportional hazards model was generated for the survival end point. QoL data were evaluated by calculating the total FACT-L score and the 21-item TOI. Scores recorded before each course of treatment were compared with baseline scores. A repeated measures analysis was performed to compare the rate of change between the 2 treatment groups for each dimension or sub-scale.

- Sample size/power calculation: based on the feasibility of patient accrual and study completion rather than on formal statistical criteria. A study population of 150 pts per treatment arm provided 71% power that the 95% CI would exclude more than 10% difference in favour of IV treatment.
- Attrition/drop-out: Numbers and reasons reported. However, discrepancy between Fig 1 and text regarding number of drop-outs for oral therapy (30 vs 31 respectively).

General comments

- Generalisability: pts with limited or extensive-stage SCLC who had documented CR or PR to first-line therapy with disease recurrence after ≥90 days. Likely to be a mixture of pts groups across a variety of countries but no details on ethnicity or demographics were given.
- Outcome measures: outcomes are appropriate but uncertain of the reliability of some results which do not have 95% CI / have wide ranges; also no p-values or statistical tests were calculated to compare treatment groups for all but 2 outcomes.
- Inter-centre variability: not reported
- Conflict of interests: supported by GlaxoSmithKline, UK. Many authors are either GSK employees or are consultants to GSK. GSK employees were involved in all aspects of the trial, including study design and data analysis. Many trial authors had potential conflicts of interest noted in the report.

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: #901 and #768 (abstract) Author: Inoue *et al.* and Sugawara *et al.* (abstract) Year: 2008 Country: Japan Study design: Phase II RCT Number of centres: 12 Funding: States 2 authors provided	Group A: Intravenous Amrubicin (A) Dose: 40mg/m^2/d Duration: 5 min infusion on days 1-3 every 3 wks Group B: Intravenous topotecan (T) Dose: 1.0mg/m^2/d Duration: 30 min infusion on days 1-5 every 3 wks Patients received at least 3 cycles (A: median 3, range 1 – 7; T: median 2, range 1-4) unless obvious disease	*Number of Participants*: 60 A = 29 T = 30 *Sample attrition/dropout:* 1 randomised A patient was not treated due to rapid disease progression; 1 treatment-related death (A group) *Sample crossovers*: cross-over for 3rd-line (or later) chemo performed in 41% of patients (A=5, T=19) *Inclusion criteria*: Patients ≥ 20yrs, histologically or cytologically confirmed diagnosis of SCLC, previously treated with platinum-based chemo regimen, ECOG PS of ≥ 2, adequate bone marrow	Primary outcomes: overall response rate (ORR) Secondary outcomes: Progression free survival (PFS), overall survival (OS) & toxicity profile. Also reports disease control rates (DCR) but data not extracted here. Methods of assessing outcomes: CT scan used to assess ORR according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Toxicity assessed according to National Cancer Institute Common Toxicity Criteria, version 2.0.

financial support	progression, patient refusal or intolerable toxicity. Other interventions used: granulocyte colony-stimulating factor permitted as a therapeutic intervention for neutropenia (but not for use as a prophylactic). Subsequent doses of A and T were reduced to 35 mg/m^2/d or 0.8 mg/m^2/d respectively if toxicities were observed (grade 4 neutropenia for ≥4 days, grade 3 febrile neutropenia, grade 4 thrombocytopenia or grade ≥ 3 non-haematologic). Subsequent chemotherapy after disease progression not limited. 14 A and 21 T received subsequent chemotherapy.	function (absolute neutrophil count ≥ 1500/mm^3, platelet count ≥ 100,000mL, Hb ≥ 9mg/dL, AST and ALT ≤ 100 IU/L, total bilirubin level ≤ 2.0 mg/dL, serum creatinine ≤ 1.5mg/dL, arterial oxygen pressure ≥ 60mmHg, ECG findings within normal range, left ventricular ejection fraction ≥ 60%), resistance to or progressive disease after 1st-line treatment, measurable disease with RECIST criteria, no chemotherapy or chest radiotherapy within 4 wks prior to enrolment. *Exclusion criteria*: Patients with symptomatic brain metastases, massive pleural or pericardial effusion requiring drainage, severe comorbidities such as uncontrolled diabetes, heart disease, infectious disease, or pulmonary fibrosis, no prior A or T chemotherapy, symptomatic interstitial pneumonitis or pulmonary fibrosis apparent on chest x-ray, history of drug allergy, lactating or pregnant or possibly pregnant women, or those willing to be pregnant. *Characteristics of participants*: Gender (M/F), n (%): A: 24 (83) / 5 (17); T 25 (83) / 5 (17), *p*=1.000 Age (yrs), median (range): A 70 (54-77); T 64 (32-78), *p*=0.195 Performance status, n (%): 0: A 14 (48); T 17 (57) 1: A 10 (34); T 9 (30) 2: A 5 (17); T 4 (13), *p*=0.731 Previous treatment: Radiotherapy: A 15 (52); T 16 (53) Platinum + etoposide: A 22 (76); T 20* (67) Platinum + irinotecan: A 7 (24); T 11* (37) Response type, n (%): Sensitive: A 17 (59); T 19 (63) Refractory: A 12 (41); T 11 (37), *p*=0.793	Length of follow-up: not stated

Comments: Refractory relapse defined as no response to 1st line chemotherapy or relapse within 90 days after completion of 1st-line chemotherapy; sensitive relapse defined as relapse at an interval of ≥ 90 days after completion of 1st-line chemotherapy. *1 pt received 1st line treatment with platinum + etoposide + irinotecan.

RESULTS

Outcomes	**Amrubicin (n=29)**	**Topotecan (n=30)**	**p value, 95% CI**
Overall survival, median (months)	8.1	8.4	*p* =0.17
Overall survival by relapse type, median (months):			

Sensitive	9.9	11.7	not reported
Refractory	5.3	5.4	not reported
Comments: The overall survival of patients who received subsequent chemo (2nd-line, 3rd-line or later) after the enrolment of this study was presented as survival curves. Additionally, reports that multivariate analysis to examine the effect of age, gender, initial clinical stage, PS, relapse type, and subsequent chemo regimens on overall survival were presented in an appendix online – data not extracted here.			
Time to progression	not reported	not reported	
Progression-free survival, median (months)	3.5	2.2	*p* =0.16
Progression-free survival by relapse type, median (months):			
Sensitive	3.9	3.0	not reported
Refractory	2.6	1.5	not reported
Overall response, % (n/N)	38 (11/29)	13 (4/30)	*p* =0.039
95% CI	21-58*	1-25†	
Response, n (%)			not reported
Complete response	0 (0)	0 (0)	
Partial response	11 (38)	4 (13)	
Stable disease	12 (41)	10 (33)	
Progressive disease	6 (21)	16 (53)	
Response according to relapse-type, % (n/N) (95% CI)**:**			
Sensitive	53 (9/17) (28-77)	21 (4/19) (6-46)	*p* =0.082
Refractory	17 (2/12) (2-48)	0 (0/11) (-28)	*p* =0.478
Response according to PS (ECOG), % (n/N) (95% CI)**:**			
0-1	42 (10/24); (22-63)	15 (4/26); (4-35)	*p* =0.059
2	20 (1/5); (1-72)	0 (0/4); (-60)	*p* =1.000
Comment: *Different from confidence intervals reported in Sugawara abstract (95% CI 20, 56); †different from confidence intervals reported in conference presentation (95% CI 4, 31). Reports that better overall response rates were observed in A group regardless of age, gender or prior chemo regimen, but data is not shown.			
Response duration	not reported		
Others	not reported		
HRQoL	not reported		

Haematological toxicity	**A**				**T**			
	Grade (n)			≥ Grade 3 (%)	Grade (n)			≥ Grade 3 (%)
	2	3	4	(%)	2	3	4	(%)
Neutropenia	0	5	23	93†	3	13	13	87
Thrombocytopenia	6	7	1	28	5	9	3	40
Anaemia	15	3	3	21	12	6	3	30
Non-haematological toxicity								
Fatigue	4	5	0	17	3	2	0	7
Febrile neutropenia	-	4	0	14	-	1	0	3
Infection	0	2	1*	10	0	1	0	3
Anorexia	4	2	0	7	4	0	0	0
Nausea/vomiting	1	1	0	3	1	0	0	0
Stomatitis	1	1	0	3	0	0	0	0
Diarrhoea	0	0	0	0	0	1	0	3
Fever	2	0	0	0	1	0	0	0
Constipation	2	0	0	0	0	0	0	0
Pneumonitis	1	0	0	0	2	0	0	0

Comments: †97 in Sugawara abstract; *1 treatment related death (grade 5) – pt died of neutropenic sepsis developing from a urinary tract infection.

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: randomisation according to stratified factor (PS 0 or1 vs 2; relapse type, sensitive vs refactory). No other details reported.

- Blinding: may have been possible due to both treatments being intravenous. Reports that extramural reviewers assessed the eligibility, assability and response of each patient. No other details reported.
- Comparability of treatment groups: groups appear comparable. Paper reports there were no statistically significant differences for demographic characteristics (p values presented in Sugawara abstract). Patients in T arm were slightly younger than those in A arm, but not significant (p=0.195).
- Method of data analysis: if response rates of subgroups defined in patient characteristics were unusually large or small, additional analyses were performed for these subgroups. 95% confidence interval (CI) was calculated using a binominal distribution. Fisher's exact test was used to estimate the correlation among different variables between arms. Survival estimation was performed using the Kaplan-Meier method and log-rank test. Step-wise multivariate analysis was used to assess the prognostic significance of several variables.
- Sample size/power calculation: it is assumed that an ORR of 40% in eligible patients indicates potential usefulness, while an ORR of 15% is the lower limit of interest, with alpha = 0.05 and beta = 0.10, the estimated accrual was 27 patients in each arm. Accrual in both groups was continued if at least 3 responses were documented in the first 16 assessable patients.
- Attrition/drop-out: details reported.

General comments

- Generalisability: population of previously treated sensitive (relapse $\geq$ 90 days after completion of 1 st-line therapy) and refractory (no response to 1st-line chemotherapy or relapse within 90 days after completion of therapy) SCLC patients. Sensitive relapse, n=36/59 (61%); refractory relapse, n=23/59 (39%). Therefore, a proportion were not responders, but this number is unknown. Also, the topotecan dose is lower than used in UK (approved dose in Japan is 1.0 mg/m^2 compared to 1.5 mg/m^2 in UK).
- Outcome measures: appropriate. However, median instead of mean reported and no SD provided.
- Inter-centre variability: not reported
- Conflict of interests: report no conflicts of interest.

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
9. Did the analyses include an intention to treat analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: #279, #5214 and #5215 (abstracts) Author: O'Brien *et al.;* Chen *et al.*, O'Brien *et al.* (abstracts) Year: 2006 and 2007 (abstracts) Country: Europe, Canada, Russia Study design: RCT	<u>Group A:</u> Oral topotecan hydrochloride + Best Supportive Care (BSC) Dose: 2.3 mg/m^2/d Duration: days 1 to 5 every 21 days according to bone marrow recovery. At least 4 treatment cycles were recommended,	*Number of Participants*: 141. Topotecan 71, BSC 70 *Sample attrition/dropout:* Topotecan 21 (30%); BSC 33 (47%). Reasons for withdrawal: Adverse event (topotecan 13 [18%]; BSC 9 [13%]); Protocol violation (topotecan 0, BSC 7 [10%]); Lost to follow-up (topotecan 2 [3%]; BSC 4 [6%]); Other (topotecan 5 [7%, patient choice 4, lack of compliance 1]; BSC 13 [19%, patient choice 6, death 2, progressive disease 2, patient moved 1, patient received terminal care at home 1, patient started 2nd-line therapy 1]); ongoing (topotecan 1 [1%]; BSC 0).	Primary outcomes: overall survival (all cause mortality) Secondary outcomes: response rate (WHO criteria), time to disease progression (TTP), Patient Symptom Assessment (PSA), QOL, safety Methods of assessing outcomes: states independent review of responses was not conducted. PSA: evaluated the degree to which participants

Number of centres: 40 Funding: sponsored by GSK (manufacturer)	depending on tolerability and response. Delays and dose adjustments were prescribed in the protocol if a number of parameters were not met (not reproduced here). Participant withdrawn if delays of more than 2 weeks at minimum dose of 1.5 mg/m^2/d. <u>Group B:</u> BSC alone. Other interventions used: all participants had equal access to supportive care measures (analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, red blood cell transfusions, deep relaxation therapy, palliative radiotherapy or surgical procedures). All therapies with potential systemic antitumour effect were excluded.	*Sample crossovers*: none. However, 13 participants in each arm (18.3% BSC, 18.6% topotecan) received poststudy chemotherapy either alone or in combination with other therapy such as radiotherapy and surgery. In addition poststudy radiotherapy alone was received by 7 (10%) topotecan participants and 1 (1%) BSC participant. *Inclusion/exclusion criteria*: only those considered unsuitable for further IV chemotherapy were recruited. Unsuitability was based on local policy in patients with resistant (short treatment-free interval, TFI) SCLC and assessed on an individual basis by the oncologist. Initially excluded were those with a TFI of > 90 days for whom treatment with BSC was not acceptable, however, during the trial, some participants with sensitive SCLC who were unsuitable for standard chemotherapy due to comorbidities or who had refused chemotherapy due to the risk of toxicity were eligible. Eligibility criteria also included extensive or limited SCLC, one prior chemotherapy regimen, age ≥ 18 years, performance status of 0, 1, or 2 (Eastern Cooperative Oncology Group scale used), haemoglobin ≥ 9.0g/dL, white blood cell count ≥ 3,500/mm^3, platelets ≥ 100,000/$mm/^3$, neutrophils ≥ 1,500/mm^3, calculated creatinine clearance ≥ 60 mL/min, serum bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and alkaline phosphatise ≤ five times upper limit of normal with liver metastases or ≤ two times without, at least 24-hours since last radiotherapy, at least 3 months since last immunotherapy. Exclusions – symptomatic CNS metastases, concomitant or previous malignancies within the last 5 years (except SCLC and adequately treated nonmelanoma skin cancer, cervical carcinoma in situ, or localised low-grade prostate cancer), infection, severe comorbidities, gastrointestinal conditions or drugs affecting gastrointestinal absorption, prior topotecan therapy, hypersensitivity or other contraindication to the study drugs. *Characteristics of participants*: Gender (M/F), n (%): topotecan 52/19 (73/27%); BSC 51/19 (73/27%) Age (yrs), mean (SD) range: topotecan 59.8 (9.0) 37-76; BSC 58.6 (8.2), 43-79	experienced nine common and clinically relevant symptoms using a Likert scale for severity (from 1 [not at all] to 4 [very much]. QOL by patient self-report using the EuroQol-5D index and EQ-5D Visual Analogue Scale (VAS) – evaluating five health status dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Rating of 1 [no problem] to 3 [extreme problem]. EQ-5D index scored on a scale from 0 (dead) to 1 (perfect health); VAS scored from 0 [worse imaginable] to 100 [best imaginable] health state. Patient self-reported lung symptoms assessed using PSALC instrument (but data not extracted here). Length of follow-up: every 2 months for the full duration of survival. Median time on study 7.8 weeks in the BSC group and 12.3 weeks in the topotecan group.

		Disease stage, n (%): Limited: topotecan 23 (32%); BSC 27 (39%) Extensive: topotecan 48 (68%), BSC 43 (61%) Performance status, n (%): 0: topotecan 8 (11%); BSC 6 (9%) 1: topotecan 44 (62%); BSC 41 (59%) 2: topotecan 19 (27%); BSC 23 (33%) Max lesion diameter (cm), n (%): <2: topotecan 7 (10%); BSC 2 (3%) 2 - <5: topotecan 34 (48%); BSC 25 (36%) 5 - 10: topotecan 19 (27%); BSC 32 (46%) >10: topotecan 2 (3%); BSC 5 (7%) Not measurable: topotecan 9 (13%); BSC 6 (9%) Previous treatment: Any prior treatment: topotecan 46 (65%); BSC 48 (69%) Radiotherapy: topotecan 38 (54%); BSC 34 (49%) Surgery: topotecan 18 (25%); BSC 20 (29%) Immunotherapy: topotecan 0; BSC 4 (6%) Cisplatin or carboplatin: topotecan 80%, BSC 77% Etoposide: topotecan 76%; BSC 74% Response, n (%): not reported Response type, n (%): not reported as such but see TFI below. TFI (time to progression since completion 1st-line therapy), days: ≤ 60: topotecan 22 (31%); BSC 20 (29%) > 60: topotecan 49 (69%); BSC 50 (71%) ≤ 90: topotecan 41 (58%); BSC 35 (50%) > 90: topotecan 30 (42%); BSC 35 (50%) Median (range): topotecan 84 (34-1,996); BSC 90 (14 – 1,409). Liver metastases, n (%) Yes/No: topotecan 20/51 (28%/72%); BSC 14/56 (20%/80%)	

RESULTS			
Outcomes	**Topotecan (n=71)**	**BSC (n=70)**	**P Value, 95% CI**
Overall survival			
Unadjusted hazard ratio (HR) for overall survival was 0.64 (95% CI 0.45, 0.90) for topotecan relative to BSC. Adjusted HR 0.61 (95% CI 0.43, 0.87). Overall survival was significantly longer in the topotecan group (log-rank p=0.01).			
Median survival time, weeks	25.9 (95% CI 18.3, 31.6)	13.9 (95% CI 11.1, 18.6)	Not tested
Six-month survival rate	49%	26%	Not tested
Subgroup analyses of survival according to stratification factors (HR and 95% CI estimated from figure to one decimal place only as scale on figure is inconsistent, so for illustration only)			
Gender, male **Female**	HR 0.8 (95% CI 0.5, 1.2) HR 0.4 (95% CI 0.2, 0.7)		
Performance status, 0/1 **2/3/4**	HR 0.7 (95% CI 0.5, 1.1) HR 0.5 (95% CI 0.3, 0.9)		

For those with a PS 2	Median survival topotecan 20.9 (95% CI 13.4, 26.9) weeks, BSC 7.7 (95% CI 5.3, 13.3) weeks.		
Time to progression, ≤ 60 days **> 60 days**	HR 0.5 (95% CI 0.3, 0.9), median survival topotecan 23.3 (95% CI 10.7, 30.9) weeks, BSC 13.2 (95% CI 7.0, 21.0) weeks HR 0.7 (95% CI 0.5, 1.1)		
Presence of liver metastases **No liver metastases**	HR 0.7 (95% CI 0.3, 1.3) HR 0.6 (95% CI 0.4, 0.9)		
Comments: Paper states that HRs and 95% CIs for all subgroups indicate a survival trend favouring topotecan, however the 95% CI cross 1.0 for TTP > 60 days, Male, PS 0/1, and liver metastases.			
Progression	59 (83%)		
Time to progression, median weeks	16.3 (95% CI 12.9, 20.0)		
Response rate (all partial responses)	5 (7%) 95% CI 2.33, 15.67	Not applicable	
Comments: response not assessed in 11 (16%) participants.			
Achieved stable disease	31 (44%)		
Progressive disease	24 (34%)		
Comments: response according to the stratification factors presented but not extracted as for topotecan group alone.			
EQ-5D, rate of deterioration per 3-month interval	-0.05 (95% CI -0.11, 0.02)	-0.20 (95% CI -0.27, -0.12)	Difference + 0.15 (95% CI 0.05, 0.25)
Comments: Baseline EQ-5D questionnaires were completed by 68 (96%) participants in the topotecan group and 65 (93%) participants in the BSC group. At least one post baseline questionnaire was completed by 63 (89%) participants in the topotecan group and 49 (70%) participants in the BSC group.			
EQ-5D Index (pooled analysis†), mean	n=239	n=167	Difference 0.09, p=0.0036
Baseline	0.72	0.68	
Treatment	0.69	0.56	
Change from baseline	-0.03	-0.12	
EQ-5D Index (change*), mean	n=61	n=51	Difference 0.2, p=0.0034
Baseline	0.70	0.65	
Treatment	0.61	0.34	
Change from baseline	-0.10	-0.30	
EQ-5D VAS (pooled analysis†), mean	n=238	n=162	Difference 7.71, p<0.0001
Baseline	66.46	67.22	
Treatment	66.76	59.80	
Change from baseline	0.30	-7.41	
EQ-5D VAS (change*), mean	n=60	n=48	Difference 10.48, p=0.0025
Baseline	65.75	64.29	
Treatment	61.77	49.83	
Change from baseline	-3.98	-14.46	
†change from baseline to averaged on-treatment assessments; *change from baseline to last evaluation analysis. O'Brien (2007) abstract presents a sub-group analysis of the association between baseline PSALC total scores and ECOG PS according to partial response or stable disease (topotecan arm only), but data not extracted.			
PSA scores	**Odds ratio**	**95% CI**	**P-value**
Shortness breath	2.18	1.09, 4.38	p<0.05
Cough	1.35	0.68, 2.66	NS
Chest pain	2.07	1.00, 4.28	NS
Coughing blood	1.95	0.46, 8.27	NS
Loss of appetite	1.02	0.57, 1.84	NS
Interference sleep	2.16	1.15, 4.06	p<0.05
Hoarseness	1.35	0.63, 2.87	NS
Fatigue	2.29	1.25, 4.19	p<0.05
Interference daily activity	1.70	0.95, 3.03	NS
Comments: Baseline questionnaires were completed by 70 participants in the topotecan group and 67 participants in the			

BSC group. The numbers of participants with sufficient data to be included in the analyses varied for the symptom scores between 47-48 for the BSC group and 60-61 for the topotecan group. OR > 1 indicates greater likelihood of symptom improvement on topotecan.

Adverse Effects	Topotecan (n=71)	BSC (n=70)	P Value, 95% CI
Toxicity, **grade 3/4 neutropenia,** **grade 3/4 throbocytopenia,** **grade 3/4 anaemia** **Febrile neutropenia**	 61% 38% 25% 3%		
Nonsepsis infection ≥ grade 2	10 (14%)	8 (12%)	
Sepsis	3 (4%)	1 (1%)	
Diarrhoea **Fatigue** **Vomiting** **Dyspnoea** **Cough**	6% 4% 3% 3% 0	0 4% 0 9% 2%	
Toxic deaths	4 (6%), 3 due to haematological toxicity		
All cause mortality within 30 days of randomisation	5 (7%)	9 (13%)	

Comments: 2 participants (3%) in the topotecan arm received Granulocyte colony-stimulating factor or Granulocyte-macrophage colony-stimulating factor and 2 (3%) received erythropoietin.

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: participants randomly assigned 1:1 using a centralised automated registration and randomisation system, stratified by gender, performance status, treatment-free interval (TFI) and presence of liver metastases.
- Blinding: blinding of outcome assessors not reported. Blinding of participants or care providers unlikely to be appropriate with these interventions. However, no discussion of why placebo-controlled double blind study not performed.
- Comparability of treatment groups: paper states participant demographics were well matched between arms, particularly with respect to the major prognostic variables of PS and sex. P-values however not reported.
- Method of data analysis: states efficacy assessments based on all randomly assigned participants using an intention to treat population. Safety and QOL were based on all who received at least one postrandom assignment evaluation on the BSC arm or one dose of topotecan (70 participants in topotecan arm, 67 in BSC arm evaluated). Overall survival analyzed using Kaplan-Meier and compared using log-rank test. Analysis of secondary outcomes were descriptive with no adjustments made for multiplicity. Response rates were summarised along with a 95% CI and TTP was summarised by Kaplan-Meier. All p-values were 2-sided. For PSA a generalised estimating equations model was fitted to longitudinal symptom data to estimate treatment effect on each symptom (response was categorised as favourable or unfavourable). Change from baseline in EQ-5D index and EQ-5D VAS assessed using a pooled analysis (change from baseline to averaged on-treatment assessments) and also considering only change from baseline to last evaluation. The rate of change in EQ-5D index score (rate at which symptoms improved or deteriorated) across treatment groups was evaluated with a longitudinal analysis using a mixed model (to account for repeated measurements over the treatment course) with change from baseline in score as response.
- Sample size/power calculation: Designed to detect a 66.7% difference in median survival. The expected survival in the BSC arm was 12 weeks, the estimated median survival in the topotecan arm was 20 weeks. Initial sample size calculations determined 220 participants were required to assess a survival benefit with topotecan with 90% power and a significance level of 0.05. However, recruitment was slower than anticipated, and a formal protocol amendment was implemented to terminate the study once 125 deaths had been reported. This provided an 80% power to assess a survival benefit for topotecan at a 0.05 significance level. This point was reached when 141 participants had been recruited.
- Attrition/drop-out: numbers and reasons provided (above)
- Other comments: 69 (99%) topotecan participants took ≥ 90% of their prescribed capsules. A median of 4 (range 1 to 10) courses of topotecan were administered. Dose reductions occurred in 16 courses (8%) primarily for haematological toxicity (13 courses, 6%). Dose delays occurred in 41 courses (20%), most commonly for haematological toxicity (25 courses, 12%). Dose escalation occurred in 39 courses (14%). The median topotecan dose intensity achieved was 3.77 $mg/m^2/wk$ representing 98% of the scheduled dose. BSC participants were observed for the equivalent of a median of 3 courses (range 1 to 13). Palliative medications and radiotherapy were used more frequently in the BSC group, while

transfusions were used more frequently in the topotecan group (data not extracted as not statistically analysed).

General comments

- Generalisability: patients with resistant disease (relapse within 90 days) only initially included, widened to include those with sensitive disease (greater than 90 days response).
- Outcome measures: unclear how valid and reliable
- Inter-centre variability: not reported whether potential inter-centre variability was an issue or how this was handled.
- Conflict of interests: supported by GlaxoSmithKline, UK, trial designed by GSK, data analysed by GSK. Many trial authors had potential conflicts of interest noted in the report.

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis? (	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: #360 Author: von Pawel *et al* Year: 2001 Country: Europe, South Africa, Australia Study design: RCT (phase II) Number of centres: 31 Funding: SmithKline Beecham	<u>Group A:</u> Oral topotecan Dose: 2.3 mg/m^2/d for 5 days every 21 days Duration: depended on response but those with stable disease recommended to have at least 4 cycles. <u>Group B:</u> IV topotecan Dose: 1.5 mg/m^2/d, 30 minute infusion for 5 days every 21 days Duration: depended on response but those with stable disease recommended to have at least 4 cycles. Other interventions used: Dose escalation permitted if no toxicity greater than grade 2, assessed by National Cancer Institute of Canada Common Toxicity	*Number of Participants*: 106; Oral 52, IV 54 *Sample attrition/dropout*: not reported *Sample crossovers*: none *Inclusion/exclusion criteria*: Patients of either sex, aged ≥ 18 years, with limited or extensive SCLC that had recurred ≥ 3 months after the end of 1st line therapy, provided only one prior chemotherapy regimen. All had partial or complete response. Measurable disease of at least 2cm in diameter, WHO performance status of no more than 2, life expectancy of at least 2 months, adequate bone marrow function (WBC count ≥ 3.5 X 10^9/L, neutrophils ≥ 1.5 X 10^9/L, platelets ≥ 100 X 10^9/L, haemoglobin ≥ 9 g/dl) and adequate renal and hepatic function (serum creatinine ≤1.5 mg/dL; bilirubin ≤ 2.0 mg/dL; alkaline phosphatase, AST, and ALT ≤ twice the upper limit of normal, or ≤ 5 times the upper limit of normal if liver metastases were present). At least 4 weeks since previous surgery and at least 24 hours since last radiotherapy. Those with brain or leptomeningeal disease, diagnosed by CT or MRI, could be included provided there were no signs or symptoms on neurological examination that could be attributed to metastases and that the patient was not receiving corticosteroid therapy to control	Primary outcomes: response, response duration, time to progression Secondary outcomes: time to response, survival, symptoms, toxicity. Methods of assessing outcomes: Response evaluated according to WHO criteria. Complete response (CR) by disappearance of measurable lesions lasting at least 4-weeks with no appearance of new lesions. Partial response (PR) by a decrease of more than 50% in measurable lesions lasting at least 4-weeks with no appearance of new lesions. Time to response measured from first dose of topotecan to first documented response. Duration of response from time when the response was first documented to disease progression. Time to progression and survival were measured from first administration of topotecan to progression or death, respectively.

	Criteria, was seen in the preceding course. For those in the oral group, daily dose increased by 0.4 mg/m^2/d (up to a maximum dose of 3.1 mg/m^2/d). For those in the IV group, daily dose increased by 0.25 mg/m^2/d (up to a maximum dose of 2.0 mg/m^2/d). For oral topotecan, dose escalation was made in 17.2% of courses, for IV topotecan dose escalation occurred in 6.3% of courses. Granulocyte colony-stimulating factor (G-CSF) for therapeutic intervention, not mandatory for prophylaxis against neutropenia for haematological toxicity. Severe or prolonged neutropenia managed through dose reduction during next course. Reduction in oral group by 0.4 mg/m^{2}d, in IV group by 0.25 mg/m^2/d. If grade 3/4 toxicity (excluding nausea or vomiting) dose reduced as above, if disease did not respond then patient withdrawn. For oral topotecan, dose reduction was made in 6.7% of courses, for IV topotecan dose reduction occurred in 16.4% of courses. Haematological toxicity lead to dose delays of ≥ 7 days in only 2.5% of courses with either regimen. Treatment also delayed if bone	symptoms. Excluded: those with previous or current malignancies at other sites, except adequately treated carcinoma of the cervix, or basal or squamous cell carcinoma of the skin. Other severe uncontrolled medical problems. *Characteristics of participants*: Gender (M/F), n (%): oral 39/13 (75/25); IV 43/11 (79.6/20.4) Age (yrs), mean (range): Oral 59.9 (38-79), IV 58.2 (35-74). Disease stage, n (%)*: Limited: Oral 14 (26.9); IV 14 (25.9) Extensive: Oral 37 (71.2); IV 39 (72.2) *Missing data for 1 participant in each group. Performance status, n (%): 0: Oral 10 (19.2); IV 18 (33.3) 1: Oral 34 (65.4); IV 21 (38.9) 2: Oral 8 (15.4); IV 15 (27.8) Max lesion diameter (cm), n (%): <2: Oral 0; IV 1 (1.9) 2 - <5: Oral 26 (50); IV 21 (38.9) 5 - 10: Oral 25 (48.1); IV 30 (55.6) >10: Oral 1 (1.9); IV 2 (3.7) Previous treatment: Response (partial: complete) not reported Response type (sensitive: resistant: refractory) not reported Time to disease progression after end of 1st-line chemotherapy, n (%) months: < 3 months**: Oral 1 (1.9); IV 1 (1.8) 3-6 months: Oral 19 (36.5); IV 19 (35.2) > 6 months: Oral 32 (61.5): IV 34 (63.0) ** treatment free interval of 11 weeks and 11.7 weeks Liver metastases, n (%): Present: Oral 16 (30.8); 17 (31.5) Absent: Oral 36 (69.2); IV 37 (68.5) Previous radiotherapy (%): Oral 71.2%, IV 72.2%	Symptoms were evaluated on a 4-point symptoms of disease scale (1= not at all, 2= a little bit, 3= quite a bit, 4 = very much). Not a validated scale although based on the Lung Cancer Symptom Score. A symptom improvement needed to be sustained until the next cycle to be reported as a response. All radiological responses confirmed by an independent review by a consultant radiologist. The reviewer was blinded as to whether participants received oral or IV topotecan. Length of follow-up: unclear, although progression was assessed up to 54 weeks and survival up to 64 weeks.

	marrow had not recovered and was a clinically significant nonhaematological toxicity to study drug.		

RESULTS			
Outcomes	**Oral topotecan (n=52)**	**IV topotecan (n=54)**	**P Value, 95% CI**
Overall survival, median	32 weeks 32.3 weeks (0.4 to 69.1)*	25 weeks 25.1 (0.6 to 65.1)*	Risk Ratio: 0.84 (95% CI 0.53, 1.32)
Comments: states that accounting simultaneously for all prognostic factors the RR of survival was 0.90 (95% CI 0.55, 1.47); *report in table which includes censored events. States that two factors (no liver metastases and lower performance status) were statistically associated with longer survival (p=0.001 and p=0.025 respectively) but no data reported, nor any data for other factors tested.			
Response rate, n(%) **Complete response** **Partial response** **Overall response**	 1 (1.9) 11 (21.2) 12 (23.1) 95% CI 11.6, 34.5	 2 (3.7) 6 (11.1) 8 (14.8) 95% CI 5.3, 24.3	Difference (overall response rate): 8.3% (95% CI -6.6% to 23.1%
Non responders, n (%) **Stable disease** **Progressive disease** **Not assessable**	 10 (19.2) 16 (30.8) 14 (26.9)	 16 (29.6) 23 (42.6) 7 (13.0)	 Not reported Not reported Not reported
Comments: states true underlying response rate with oral topotecan is at worst 6.6% lower than that of the IV topotecan, which is not a clinically meaningful difference. States that two factors (female gender and no previous radiotherapy) were statistically associated with increased probability of response (p=0.021 and p=0.015 respectively) but no data reported, nor any data for other factors tested. Accounting simultaneously for all prognostic factors identified in the logistic regression analysis (data not reported), oral topotecan participants 1.6 times more likely to respond than IV participants (95% CI for the odds ratio: 0.50, 5.15).			
Response duration, median	N=12 18 weeks	N=8 14 weeks	Not reported
Time to progression, median (range)	N=52 15 (0.4 – 69.1) weeks	N=54 13 (0.6 – 65.1)* weeks	Risk ratio: 0.90 (95% CI 0.59, 1.39)
Comments: regression modelling of time to progression identified female gender (p=0.041), no liver metastases at baseline (p=0.020) and lower performance status (p=0.036) as associated with longer time to progression. No data were reported for these or any other factors tested in the model. Accounting for all prognostic factors simultaneously the RR of progression was 0.98 (95% CI 0.63, 1.54). *includes censored events.			
Symptom reduction (in those with symptom at baseline) **Chest pain** **Shortness of breath** **Cough** **Haemoptysis** **Anorexia** **Insomnia** **Hoarseness** **Fatigue** **Interference daily activity**	n/N (%) 8/19 (42.1) 4/29 (13.8) 5/31 (16.1) 1/3 (33.3) 5/27 (18.5) 8/25 (32.0) 5/14 (35.7) 7/33 (21.2) 8/31 (25.8)	n/N (%) 7/22 (31.8) 9/33 (27.3) 8/36 (22.2) 4/10 (40.0) 9/29 (31.0) 8/27 (26.6) 9/24 (37.5) 6/36 (16.7) 8/36 (22.2)	Not reported
Comments: n = number with improvement, N = number with symptom at baseline. Therefore only a sub-group. Improvement represents improvement for two consecutive assessments after baseline.			

Adverse Effects	**% participants Oral**		**% participants IV**		Difference grade 4 oral:IV
Toxicity grade 3, grade 4	Grade 3	Grade 4†	Grade 3	Grade 4	Grade 4 neutropenia
Neutropenia	21.6	35.3	26.9	67.3	p=0.001.
Leucopenia	27.5	17.6	45.3	28.3	no reports of testing
Thrombocytopenia	25.5	27.5	24.5	24.5	others for statistical
Anaemia	27.5	3.9	26.4	3.8	significance
Comments: 52 participants in the Oral group received a total of 215 courses of treatment, the 54 IV participants received a total of 213 courses of treatment. In both groups a median of four courses per participant were received (range 1-12). The major reason for early discontinuation of treatment was occurrence of adverse experiences.					

†Two participants (1.9%) in the oral topotecan group died of sepsis and febrile agranulocytosis.
Median duration of grade 4 neutropenia was similar (Oral group 7 days, IV group 6 days).
Data on toxicity by number of courses of the respective therapies not data extracted.
G-CSF was administered as a treatment of neutropenia for 3 (5.8%) participants in the oral group and 4 (7.4%) participants in the IV group.
At time of analysis, 85 participants had died, 73 due to progressive disease.

Adverse effects occurring in ≥ 5% participants, n(%)	**Oral**			**IV**			
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Not reported
Vomiting	6 (11.5)	0	0	2 (3.7)	0	0	
Dyspnoea	5 (9.6)	0	0	5 (9.3)	0	1 (1.9)	
Fever	2 (3.8)	1 (1.9)	1 (1.9)	1 (1.9)	0	0	
Pneumonia	3 (5.8)	1 (1.9)	0	0	0	1 (1.9)	
Diarrhoea	4 (7.7)	0	0	0	0	0	
Pulmonary embolism	1 (1.9)	0	2 (3.8)	0	0	1 (1.9)	
Asthenia	3 (5.8)	0	0	5 (9.3)	0	0	
Fatigue	3 (5.8)	0	0	1 (1.9)	0	0	
Alopecia	1 (1.9)	0	0	7 (13.0)	0	0	
Abscess	0	0	0	2 (3.7)	1 (1.9)	0	

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: states randomised but no further details. Enrolment was stratified by the extent of disease (limited, extensive), duration of response to chemotherapy after cessation (3-6 months, ≥ 6 months) and liver metastases (presence or not).
- Blinding: reports that reviewer blinded to participant group, unclear if this relates just to the radiological outcomes or all outcomes.
- Comparability of treatment groups: states demographic imbalance between the two groups was generally negligible and was accounted for in the multivariate comparisons of treatment regimens. Baseline characteristics relating to extent of disease appear imbalanced on some factors (performance status, lesion diameter).
- Method of data analysis: objective radiological response rates were calculated along with 95% CI. Cox proportional hazards regression was used for time to event variables, logistic regression and Cox proportional hazards models for subgroup analyses (duration, ≤ 6 months, > 6 months; gender, renal impairment, performance status 0 or 1 versus 2 or 3, liver metastases, extent of disease, previous radiotherapy, maximum tumour diameter≤ 5 cm versus > 5 cm) on response and time to event variables respectively (data not reported). States all those entering the study were included in the intention-to-treat analysis.
- Sample size/power calculation: study was designed to give an indication as to the number of participants required in a phase III study of a similar design. To indicate both risk and benefit a study of 100 participants was considered the most appropriate, but no official sample size calculation was provided.
- Attrition/drop-out: no flow chart provided, no discussion numbers or reasons for attrition.

General comments

- Generalisability: population of relapsed SCLC, minimal demographic detail reported.
- Outcome measures: appropriate, although symptom score not validated
- Inter-centre variability: not reported
- Conflict of interests: sponsored by a grant from SmithKline Beecham pharmaceuticals. Three authors are employees of SKB.

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	Inadequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Adequate

10. Were withdrawals and dropouts completely described?	Inadequate

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #378 & #736 (abstract) Author: von Pawel *et al* & Schiller *et al* (abstract) Year: 1999 & 1998 (abstract) Country: Germany, Canada, France, UK, USA Study design: RCT Number of centres: unknown Funding: SmithKline Beecham	Group A: topotecan (T) Dose: 1.5 mg/m^2/d as 30 min infusion Duration: 5 consecutive days every 21 days Group B: cyclophos-phamide (C), doxorubicin (D) & vincristine (V) (CAV) Dose: C 1000mg/ m^2 (max 2000mg), + D 45mg/m^2 (max 100 mg) +V 2mg infusion Duration: day 1 of each 21-day course Full dose if on treatment day neutrophil count ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L + Hb count ≥ 9.0gm/dL. T could be escalated to max dose 2.0 mg/m2 in absence of grade ≥2 toxicity. Patients whose best response was stable disease after 4 courses could be removed from study or continue at investigator's discretion. Patients whose disease progressed were removed from study. Patients in both grps were withdrawn if delay >2 weeks caused by persistent toxicity at min. doses. Patients with complete (CR) or partial response (PR) to therapy continued treatment until disease progression or unacceptable toxicity occurred, or for at least 6 courses past the maximal response. T reduced by 0.25 mg/m^2/d and C/D reduced by 25% for: grade 4 neutropenia complicated by fever or infection or	Number of Participants: 211 T: n = 107, CAV n = 104 *Sample attrition/dropout*: total number of dropouts not reported and unclear from text (p. 664 reports 20 withdrawal, p.661 reports 16) 20 withdrawals due to treatment-related toxicity: 10 T (9.3%) and 10 CAV (9.6%). 16 patients (7 T & 9 CAV) were withdrawn either at patient's or investigator's request from study because of treatment-related toxicity (haematologic toxicity and associated sequelae). Non-haematological reasons: 1 T patient had tumour lysis syndrome and requested withdrawal and 2 CAV patients with a decline in cardiac status. Study also reports that 1 T and 2 CAV patients were removed for lack of clinical benefit, but did not have radiologic evidence of disease progression. *Sample crossovers*: N/A Inclusion criteria: • Documented progressive, limited or extensive SCLC with date of progression at least 60 days after completion of 1st-line chemotherapy • At least 1 legion bi-dimensionally measurable by CT, MRI, ultrasound, radiograph, photograph or physical examination • Min. 4 weeks between prior surgery or immunotherapy and study entry • Min. 24 hours between radiotherapy and initiation of study drugs • Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 • Hb ≥ 9.0 g/dL • WBC count ≥ 3.5 x 10^9/L • Neutrophils ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Bilirubin ≤ 2.0 mg/dL • Transaminase and alkaline	Primary outcomes: response rate (RR) and duration of response. Secondary outcomes: time to progression, time to response, survival and improvement of disease-related symptoms. Methods of assessing outcomes: Responses were determined according to WHO criteria. Standard response criteria were used, duration of response measured from time of initial documented response to 1st sign of disease progression. Time to progression was measured from time of 1st study drug to documented progressive disease (or initiation of subsequent chemotherapy). Time to response and survival measured from time of 1st study drug to initial response and death, respectively. Symptom scores evaluated for dyspnea, cough, chest pain, haemoptysis, anorexia, insomnia, hoarseness, fatigue and interference with daily activity; improvement had to be sustained for 2 consecutive courses. Symptom evaluation included time to symptom worsening as defined by interval from 1st dose of medication until 1st evidence of worsening in post baseline assessment. Non-validated, symptom specific "symptoms of disease" SCLC questionnaire used at screening und before each course of treatment, scored on 4-point scale (1= not at all, 2= a little bit, 3= quite a bit, 4= very much).

	lasting ≥ 7 days, grade 3 neutropenia lasting > 21 days of treatment cycle or grade 4 thrombocytopenia. Same dose reduction for grade 3 or 4 non-haematologic toxicity (excl. grade 3 nausea) or patient could be withdrawn from study. Min. dose topotecan 1.0mg/m^2/d. D discontinued or patient withdrawn from study once lifetime max-tolerated dose of D (450 mg/m^2) or comparable dose of epirubicin (900mg/m^2) reached or signs of cardio-myopathy evident. D + V dose reductions were required for bilirubin or serum transaminase elevations. V dose reduction of 25% required for grade 2 neurologic toxicity: V eliminated for grade 3 - 4 neurologic toxicity until toxicity resolved. Min. dose C, D + V set by administering physician. Other interventions used: Granulocyte colony-stimulating factor (G-CSF) at discretion of investigator.	phosphatase values ≤ 2 x upper limit of normal (ULN) (or if liver metastases present ≤ 3 ULN) • Creatine ≤ 1.5 mg/dL or creatine clearance ≥ 60mL/min. Exclusion criteria: • Symptomatic brain metastases requiring corticosteroids or pre-existing cardiac disease (including clinical congestive heart failure, arrhythmias requiring treatment or a myocardial infraction within preceding 3 months) • Contraindicated CAV (including history of demyelinating polyneuropathy or poliomyelitis) • Lifetime cumulative dose of doxorubicin > 270 mg/m^2 or cumulative dose of epirubicin > 540 mg/m2 • Prior topotecan therapy or >1 previous chemotherapy regimen *Characteristics of participants*: Age: not reported Gender (% male): T 57%, CAV 68% Disease stage, n (%): Limited: T 18 (16.8), CAV 16 (15.4) Extensive: T 89 (83.2), CAV 88 (84.6) Performance status, n (%): 0: T 18 (16.8), CAV 20 (19.2) 1: T 64 (59.8), CAV 64 (61.5) 2: T 25 (23.4), CAV 20 (19.2) Max lesion diameter (cm), n (%): <2: T 2 (1.9), CAV 1 (1) 2 - <5: T 53 (49.5), CAV 49 (47.1) 5 - 10:T 46 (43), CAV 47 (45.2) >10:T 4 (3.7), CAV 4 (3.8) Missing: T 2 (1.9), CAV 3 (2.9) Previous treatment, n (%): Radiotherapy: T 66 (61.7), CAV 58 (55.8) Immunotherapy: T 0, CAV 2 (1.9) Surgery: T 15 (14), CAV 29 (27.9) Brain irradiation: Yes: T 27 (25.2), CAV 24 (23.1) No: T 80 (74.8), CAV 80 (76.9) Platinum (cis or carbo)/etoposide: T – T 55 (51.4), CAV 46 (44.2) CAV – T 1 (0.9), CAV 1 (1.0) Both platinum/etoposide + CAV: T 13 (12.1), CAV 17 (16.3) Cyclo/doxo/eloposide: T 20 (18.7),	Safety assessment: min. weekly complete blood cell counts, bloo chemistries on day 15 of each course and urinalysis each cycle. Electrocardiogram and multiple gated acquisition or echocardiogram performed prior and at end of treatment. Quantitative haematologic non-haematologic toxicities were assessed prior each cycle according to National Cancer Institute Common Toxicity Criteria. Length of follow-up: minimum 4 courses for patients with stable disease, ≥ 6 courses for patients with CR or PR

		CAV 16 (15.4) Vincristine/platinum (cis or carbo)/etoposide: T 4 (3.7), CAV 6 (5.8) Other regimes: T 14 (13.1), CAV 18 17.3) Response, n (%): Partial: T 60 (56.1), CAV 60 (57.7) Complete: T 47 (43.9), CAV 43 (41.3) Stable: T 0, CAV 1 (1) Response type, n (%): Sensitive: T 100%, CAV 100% Resistant: 0 Refractory: 0 Duration of response to 1st-line chemotherapy, median (range) weeks: T 24.4 (7.6-430.6), CAV 22.9 (8.7-156.7) Liver metastases, n (%): Present: T 43 (40.2), CAV 42 (40.4) Absent: T 64 (59.8), CAV 62 (59.6) Brain metastases, n (%): Present: T 12 (11.2), CAV 25 (24.0) Absent: T 95 (88.8), CAV 79 (76.0)	

Comments: Prior treatment - T 77%, CAV 79% received 1st-line regimen containing both etoposide & platinum (cisplatin or carboplatin); T 97%, CAV 97% received a regimen containing etoposide; T 38%, CAV 43% received regimen including cyclophosphamide and an anthracycline. A total of 444 courses of T (n = 107) & 359 of CAV (n = 104) administered (dose-intensity was calculated as the sum of daily doses delivered during the course dived by the duration of the course in weeks). Target doses were maintained for T (76%) & CAV (77%) of treatment course. Treatment delays beyond 1 week occurred both in T (7.1%) & CAV (5.5%) courses.

RESULTS

Outcomes	**T (n= 107)**	**CAV (n= 104)**	**P Value, 95% CI**
Overall survival, median wks, (range):	25 (0.4-90.7†)	24.7 (1.3-101.3)	NS (p = 0.795)
6 months survival, %	46.7	45.2	
12 months survival, %	14.2	14.4	
Comments: at analysis, 11.2% T & 12.5% CAV patients were censored for survival. Risk ratio of T to CAV 1.039. Baseline performance status & extent of disease statistically significant prognostic factor for survival ($p < 0.001$). In addition to stratification factors (extent of disease + performance status at baseline), gender, baseline liver metastases and baseline brain were metastases statistically significant factors for survival ($p < 0.05$); after adjustment for covariates, the effect of treatment was not statistically significant (risk ratio 1.17; p = 0.322). †censored event			
Time to progression, median wks (range)	13.3 (0.4-55.1)	12.3 (0.1-75.3†)	NS (p = 0.552)
Comments: †estimate corresponds to a censored event			
Progression-free survival	Not reported		
Overall response rate, n (%)	26 (24.3) (95% CI, 16.2 - 32.4)	19 (18.3) (95% CI, 10.8 – 25.7)	p = 0.285, (difference = 6.0%, 95% CI, 6-18)
Complete response	0	1 (1)	
Partial response	26 (24.3)	18 (17.3)	
Non-responders, overall	81 (75.7)	85 (81.7)	
Stable disease	21 (19.6)	12 (11.5)	
Progressive disease	49 (45.8)	55 (52.9)	
Not assessable	11 (10.3)	18 (17.3)	

Response rate F : M	30.4% : 19.7%	30.3% : 12.7%	
Response rate for relapse patients (60-90 days after 1st-line treatment) n (%)	3/22 (13.6)	1/21 (4.8)	
Response duration, median wks (n, range)	14.4 (n=26, 9.4-50.1)	15.3 (n=19, 8.6-69.9) †	NS (p = 0.300)
Comments: the 95% CI for the difference in the rates of response (6%) was 6 – 18. 3 T & 5 CAV patients were reported as responders, but the responses were not confirmed after independent radiological review. Of the 11 T and 18 CAV patients with an overall response of "not assessable" and classified as non-responders, 2 T and 3 CAV patients were ineligible and 5 patients were not evaluated for response (1 T patient relocated to nursing home, 2 CAV patients were lost to follow-up, 1 CAV patient died suddenly as a result of an unrelated cause & 1 CAV patient without lesion assessment after course 2). Response rate for 1st-line regimen (including cyclophosphamide & an anthracycline) T 26.8% (n=41) & CAV 20% (n=45). A logistic regression model (evaluating the effect of baseline characteristics) identified presence of baseline liver metastases and gender as the only significant factors of response (p = 0.043 and p = 0.008 respectively); after adjusting for the co-variates, T patients showed a greater propensity to respond than CAV patients, although the result was not statistically significant (odds ratio 1.24, p = 0.557). Paper also reports response rates due to 1st line chemotherapy regimen, but data not extracted here. †censored event			
Time to response, median wks (n, range)	6 (n=26, 2.4-15.7)	6.1 (n=19, 5.4-18.1)	NS (p = 0.953)
Improvement in disease-related symptoms, n/N* (%):			Pearson χ^2
Dyspnea	19/68 (27.9)	4/61 (6.6)	0.002**
Cough	17/69 (24.6)	9/61 (14.8)	0.160
Chest pain	11/44 (25.0)	7/41 (17.1)	0.371
Haemoptysis	4/15 (26.7)	4/12 (33.3)	0.706
Anorexia	18/56 (32.1)	9/57 (15.8)	0.042**
Insomnia	19/57 (33.3)	10/53 (18.9)	0.085
Hoarseness	13/40 (32.5)	5/38 (13.2)	0.043**
Fatigue	16/70 (22.9)	6/65 (9.2)	0.032**
Interference with daily activity	18/67 (26.9)	7/63 (11.1)	0.023**
Comments: Significant differences in length of time to worsening of dyspnea (p=0.046) and anorexia (p=0.003), with symptoms progressing more slowly in the T group. Verbatim terms used in questionnaire: "shortness of breath" (dyspnea), "coughing up blood" (haemoptysis) "loss of appetite (anorexia), and "interference with sleep" (insomnia). *number of patients with baseline and at least one post-baseline assessment. Improvement defined as 2 consecutive improvements over the baseline assessment. **p< 0.05.			

Adverse Effects, n/N* (%):	**T**		**CAV**	
Haematologic toxicities	Patients (n=107)	Courses (n=446)	Patients (n=104)	Courses (n=359)
Leukopenia grade 3	57/104 (54.8)	196/441 (44.4)	38/101 (37.6)	160/351 (45.6)
Leukopenia grade 4	33/104 (31.7)	68/441 (15.4)	44/101 (43.6)	77/351 (21.9)
Neutropenia grade 3	19/104 (18.3)	137/439 (31.2)	15/99 (15.2)	71/348 (20.4)
Neutropenia grade 4	73/104 (70.2)	166/439 (37.8)**	71/99 (71.7)	179/348 (51.4)**
Thrombocytopenia grade 3	30/104 (28.8)	83/441 (18.8)	10/101 (9.9)	17/350 (4.9)
Thrombocytopenia grade 4	30/104 (28.8)	43/441 (9.8)	5/101 (5.0)	5/350 (1.4)
Anaemia grade 3	41/104 (39.4)	73/440 (16.6)	18/101 (17.8)	23/351 (6.6)
Anaemia grade 4	3/104 (2.9)	5/440 (1.1)	2/101 (2.0)	2/351 (0.6)
Comments: *represents the total number of patients and courses with laboratory data available. **p<0.001 for courses. Incidence of grade 4 thrombocytopenia (p<0.001) and grade 3/4 anaemia (p<0.001) was significantly higher in T patients. Median duration of grade 4 neutropenia in both treatment groups was 7 days. RBC transfusions administered to 53.2% of T patients in 24.7% of courses vs 26.9% of CAV patients in 24.7% of courses (p < 0.001). No evidence of cumulative toxicity for T patient group. Infections occurred within 2 days of grade 4 neutropenia in 28% (30/107) of T patients and 8.7% (39/446) of courses, and in 26% (27/104) of CAV patients and 12.8% (46/359) of courses. 4.7% of T patients (1.1% of courses) and 4.8% of CAV patients (1.4% of courses) were associated with sepsis.				
Deaths (treatment related haemoatolgic toxicity with sepsis)	4		3	
Comments: a further 2 deaths were possibly related or related to therapy. 1 T death caused by acute respiratory insufficiency, 1 T deaths caused by an intracerebral haemorrhage into brain metastases reported as secondary to topotecan-induced thrombocytopenia. 1 CAV death caused by progressive disease coincident with reported CAV-related renal failure				

and pancytopneia.

Related or possibly related non-haematologic toxicities occur. in >10% of patients, n (%)	**T (n= 107)**			**CAV (n= 104)**		
	Common toxicity criteria grade					
	1/2	3/4	Total	1/2	3/4	Total
Nausea	38 (35.5)	4 (3.7)	42 (39.3)	36 (34.6)	6 (5.8)	42 (40.4)
Alopecia*	38 (35.5)	0 (0)	38 (35.5)	23 (22.1)	0 (0)	23 (22.1)
Fatigue	23 (21.5)	5 (4.7)	28 (26.2)	26 (25.0)	9 (8.7)	35 (33.7)
Vomiting	24 (22.4)	2 (1.8)	26 (24.3)	22 (21.1)	3 (2.9)	25 (24.0)
Anorexia	19 (17.7)	1 (0.9)	20 (18.7)	20 (19.2)	3 (2.9)	23 (22.1)
Stomatitis	13 (12.2)	2 (1.8)	15 (14.0)	12 (11.5)	1 (1)	13 (12.5)
Diarrhoea	12 (11.2)	1 (0.9)	13 (12.1)	13 (12.5)	0 (0)	13 (12.5)
Fever**	11 (10.3)	2 (1.9)	13 (12.1)			
Constipation				16 (15.4)	0 (0)	16 (15.4)
Asthenia				10 (9.6)	4 (3.8)	14 (13.5)
Left ventricular ejection fraction			2/26 (7.7%)			6/35 (17.1%)

Comments: dose reductions for non-haematologic toxicity occurred in 1 T patient (0.9%) due to grade 3 fatigue and in 11 CAV patients (10.6%), 9 due to neurotoxicity (p=0.003). Incidence of worsening of left ventricular ejection fraction (LVEF) was based on echocardiogram or multiple gated acquisition results and can see this from data in table (100 T and 97 CAV baseline assessments).

* reflects the number of patients who developed alopecia on study, approx. 30% in each arm presented to study with alopecia secondary to prior chemotherapy. **excludes febrile neutropenia.

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups: patients stratified by extent of disease and performance status at baseline and randomised to treatment by a telephone randomisation system.
- Blinding: all claimed responses were reviewed by an independent radiologist blinded to all claimed responses, but it is unclear whether this was the case for all outcome measures. Blinding of care providers or patients was not reported. No discussion of why a double-blind study was not performed.
- Comparability of treatment groups: paper states that stratified randomisation ensured that the distribution of 2 prognostic variables, baseline performance status and extent of disease were comparable between treatment groups. Paper states baseline characteristics were comparable between treatment groups – not supported statistically (no p values), but groups do appear comparable for most characteristic, except incidence of prior surgery (14%T vs 28% CAV). Gender (T 43% women vs CAV 32%, p = 0.091) and documented brain metastases (T 11.2% vs CAV 24.0%, p = 0.044) were not comparable between groups.
- Method of data analysis: paper states that all patients who received a dose of study medication were included in the efficacy evaluations. 2 prognostic variables, baseline performance status and extent of disease included in multivariate analytical models for time-to-event outcomes. Subgroup analysis included response by gender and time to progression relative to 1st-line chemotherapy. 95% confidence intervals (CI) for response rates (RRs) and estimated % difference in RRs between treatment groups were calculated. Kaplan-Meier survival estimates used for time-to-event variables, including time to response, response duration, time to progression and survival. Time-to-event outcomes were also compared using Cox regression model, Multivariate statistical methods applied to survival and response to determine other possible prognostic factors such as gender, performance status extent of disease, age, presence of baseline brain and/or liver metastases, response to 1st-line therapy (CR or PR), response duration and time to progression from 1st-line therapy. As baseline groups were not balanced with respect to the additional covariate, results were adjusted for the stratification variables only. For each of the symptoms of disease, Pearson's uncorrected χ^2 statistics was used to compare % of patients in each treatment grp experiencing sustained improvement over baseline (patients had to have both baseline and post baseline). For missing baseline measurements and at least 1 non-missing post baseline measure of "a little bit" or worse, baseline value was imputed as "not at all" and the patient was included in analysis of that symptom. If symptom assessments not recorded, algorithms were used to impute scores for the course with missing assessments. Kaplan-Meier estimates were obtained and tested using log-rank test for the time to worsening for each symptom. Time to symptom worsening defined as the interval from 1st dose of study drug until increase in post baseline assessment score. Patients without worsening of that symptom were censored at their last symptom assessment.
- Sample size/power calculation: not reported.
- Attrition/drop-out: reported numbers do not add up or is unclear (see column 3, p.1). Breakdown of numbers and reasons not given.

General comments

- Generalisability: patients with progressive, limited or extensive SCLC. Paper reports that study was to focus on the sensitive population (relapse >90 days after 1st-line chemotherapy, but included patients with date of progression≥ 60 days after completion of 1st-line chemotherapy.
- Outcome measures: primary and secondary measures are appropriate, but it is unclear how valid and reliable other measures are. No mean or standard deviation reported.
- Inter-centre variability: number of centres not reported and issues around inter-centre variability not discussed.
- Conflict of interests: trial supported by SmithKline Beecham and four trial authors were employees of SmithKline Beecham.

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Partial

Appendix 7: List of excluded studies

Excluded trials:	Reason for exclusion:
1. Chen,L.; Antras,L.; Neary,M.; Dharan,B.; O'Brien,M.E. Symptom assessment in small cell lung cancer (SCLC) in a randomized trial: A psychometric analysis of Patient Symptom Assessment in Lung Cancer (PSALC). *Journal of Clinical Oncology* 2007;25(18 Supplement): 18101.	Not an RCT
2. Dy GK, Jett JR, Geoffroy FJ, Krewer KD, Tazelaar H, Maurer M *et al*. Topotecan and paclitaxel in previously treated patients with relapsed small cell lung cancer: phase II trial of the North Central Cancer Treatment Group. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer* 2006;1:211-7.	Did not include the right intervention
3. Eckardt JR, Ramlau R, Gervais R, Shepherd F, O'Brien M, Ciuleanu T, Dharan B, Wissel P and Ross G. Compliance with oral topotecan in patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). *Journal of Clinical Oncology* 2006;24(18 Supplement):7092.	Not an RCT
4. Gormley N, Edelman MJ, Smith R, Hausner PF, Bedor M, Bisaccia S. Phase II trial of docetaxel and topotecan in recurrent and extensive small cell lung cancer. *Lung Cancer* 2004;46:S42-S43.	Not an RCT
5. Jotte RM, Reynolds CH, Conkling P, Oliver JW and Allen A. A randomized phase 2 trial of amrubicin compared to topotecan as second-line treatments in extensive disease small cell lung cancer (SCLC) sensitive to platinum-based first-line chemotherapy. *Journal of Clinical Oncology* 2007;25(18 Supplement):18064.	Abstract – not enough information on methodology
6. Jotte RM, Conkling PR, Reynolds C, Allen AR and Oliver JW. A randomized phase II trial of amrubicin (AMR) vs. topotecan as second-line treatment in extensive-disease small-cell lung cancer (SCLC) sensitive to platinum-based first-line chemotherapy. *Journal of Clinical Oncology* 2008;26(May 20 Supplement):8040.	Abstract – not enough information on methodology
7. Jotte RM, Reynolds C, Conkling PR, Jungnelius U and Oliver J. Amrubicin (Amr) vs topotecan as second-line treatment of extensive-disease small cell lung cancer (SCLC) sensitive to platinum-based first-line chemotherapy: A randomized phase 2 trial. *Annals of Oncology* 2008;19:116.	Abstract – not enough information on methodology
8. O'Brien ME, Duh M, Chen L, Antras L, Neary M, Dharan B and Gralla RJ. Is symptom improvement in patients with small cell lung cancer (SCLC) associated with clinical response? An analysis using the Patient Symptom Assessment Lung Cancer (PSALC) scale in a randomized trial comparing oral topotecan (OT) with best supportive care (BSC). *Journal of Clinical Oncology* 2007;25(18 Supplement): 7725.	Not an RCT
9. Peacock NW, Hainsworth JD, Switzer AB, Burris HA, Barrett C, Nicolau MF and Greco FA. Weekly bolus topotecan as secondary therapy in extensive stage small cell lung cancer: A Minnie Pearl Cancer Research Network phase II trial. *Journal of Clinical Oncology* 2004;22(14 Supplement):7278.	Not an RCT
10. Ruotsalainen, Mattson Ta, K. Topotecan (T) as second-line therapy following ifosfamide-carboplatin-etoposide (ICE) and maintenance for small cell lung cancer (SCLC). *Lung Cancer* 2000;29(9 Supplement 1):217.	Not an RCT

Appendix 8: Tabulation of the critical appraisal of the manufacturer's submission against Drummond and colleagues' checklist.[66]

Table 1 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	Cost effectiveness of oral topotecan plus BSC compared with BSC alone for people with relapsed SCLC, for whom re-treatment with first-line regimen is not considered appropriate, and who are unable or unwilling to receive IV chemotherapy
Is there a clear description of alternatives?	Yes (see Rationale section at beginning of chapter 4 of MS)	• CAV excluded as "topotecan (IV and oral) would not provide a cost effective alternative to CAV in the majority of patients given its relatively higher acquisition cost" • "compared with oral topotecan the IV formulation has a similar efficacy profile but a higher acquisition and administration costs associated. Thus, it is unlikely to be a cost effective alternative to oral topotecan" • The economic evaluation therefore focuses only on the use of oral topotecan in relapsed SCLC patients who are not considered as candidates for standard intravenous therapy with CAV, and for whom BSC represents the main option in the absence of suitable alternative therapies
Has the correct patient group / population of interest been clearly stated?	?	Scope states population as "adults with relapsed SCLC, for whom re-treatment with first-line regimen is not considered appropriate". Does not make reference to those unable or unwilling to receive IV chemotherapy – however this was part of inclusion criteria for O'Brien and colleagues RCT.[57]
Is the correct comparator used?	?	BSC would be appropriate comparator for patients identified as unsuitable or unwilling to receive standard chemotherapy, having progressed following first-line treatment (and unsuitable for re-treatment with first-line). Appropriate given the inclusion criteria for O'Brien and colleagues RCT,[57] but at variance with scope.
Is the study type reasonable?	Yes	Cost-utility analysis suitable – takes into account life expectancy differences (e.g. median OS of 13.9 and 25.9 weeks for BSC and TP respectively) and QoL differences (deterioration of 0.20 vs 0.05 over 3 month interval for BSC and TP respectively) documented in main trial publication.
Is the perspective of the analysis clearly stated?	Yes	NHS and PSS for costs (though PSS costs not explicit included other than in sensitivity analysis) Patient perspective for outcomes – overall survival weighted for quality of life.
Is the perspective employed appropriate?	Yes	• Costs: Only NHS costs included, no PSS costs included. As major difference between groups expected to relate to monitoring and administration costs incurred in NHS setting, then focus on NHS rather than PSS seems appropriate. However some discussion in sensitivity analysis on inclusion of PSS costs for palliative care. • Outcomes: Patient perspective adopted; overall survival, quality of life weights based on patient responses to EQ-5D (over 12 3-

		week periods, i.e. maximum follow up of 36 weeks) with values from population survey (Dolan and colleagues[80]).
Is effectiveness of the intervention established?	Yes	Effectiveness data are taken directly from O'Brien trial. Patient level data, recording: • survival (days from randomisation till death, unclear on censoring, other than those still alive at final follow up [reported as six, three in each arm] who were assumed to die the following day); • quality of life is measured using EQ-5D. Questions raised during review of MS on imputation for missing utility values and effects of LOCF.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	The model has used survival as observed in the study – patients who were still alive at last follow up were assumed to die the following day. May underestimate life expectancy – may have greater effect on oral topotecan and BSC group. Unlikely to bias in favour of BSC.
Are the costs and consequences consistent with the perspective employed? *Covered in detail in questions below*	Yes	Costs reported as using NHS and PSS perspective. All included costs are NHS – application of an uplift for PSS costs used in sensitivity analysis. Approach to costing is to only include treatment costs for topotecan patients, on the assumption that costs of supportive care/ symptom control are the same for both arms. Referred to in text as "a conservative approach" (MS page 90). O'Brien and colleagues trial report stated that "palliative care and radiotherapy were used more frequently in BSC" (page 5444 of journal publication) - see also Table 3 of journal publication. Suggests that excluding BSC is unlikely to bias results in favour of BSC. Categories of included cost are: • drug acquisition costs of £2,500 (using total dose per in mg per m^2 BSA and patient BSA from trial dataset to get total mg per patient). Drug costs £30 per mg [sourced from November MIMS, BNF price not available when MS submitted]); • drug administration costs of £713 (assuming patients attend secondary care to receive drugs once per cycle and unit costs of £180.43 for delivery of exclusively Oral Chemotherapy from "TCHEMTHPYOP" worksheet on NHS Reference Costs 2006/7 plus £0.90 dispensing fee giving a cost of 181.33 per cycle, for a mean of 3.93 cycles); appears reasonable. • monitoring costs of £39.30 (assuming £10 per cycle for a mean of 3.93 cycles); maybe low. Does not include imaging (Chest Xray or CT) while on-treatment • monitoring of patients from treatment cessation till disease progression of £758 (assuming an out-patient attendance every 4 weeks, GP visit every 4 weeks, chest X-ray every 4 weeks and blood tests every 4 weeks. Unit costs were £190.51 per out-patient attendance (source), £34.27 per GP visit (source), £28.22 per chest X-ray (source) and £3.02 per blood test(source). Cost of £9.14 per non-PD day for a mean of 82.9 days); chest X-ray for non-treated patients maybe excessive. Clinical advisors suggest only use CXR

		or CT when patients become symptomatic. • costs of treating toxicity –costing non-haematological toxicity on basis of reported occurrence (with unit costs estimated by experts) while haematological toxicity has been costed on the basis of transfusions, GCSF and systemic antibiotic use. Usage as reported in trial. Costs are reported as composite (as incremental costs in Table 4.5 of MS and in bottom row of Table 4.4) and by each major component (in Table 4.4 of MS). Outcomes – appropriate to lifetime horizon, using survival (days) and weighting by utilities derived from patients and valued using (UK population) tariff.
Is differential timing considered?	Yes	MS states that 3.5% discount rate has been applied, but with majority of survival below one year, this has little effect.
Is incremental analysis performed?	Yes	Costs of topotecan acquisition/ administration/ monitoring and treatment of toxicity, plus costs of non-progressive days (after finishing topotecan treatment) are only costs included. No costs included for BSC. Incremental life years and incremental QALYs are calculated and ICERs presented for both LYs gained and QALYs gained.
Is sensitivity analysis undertaken and presented clearly?	Yes	Deterministic sensitivity analyses were undertaken on: • monitoring costs (from halving to doubling monitoring costs) **little variability** (26,740-27,019); • discount rates (see above comment on relevance of discounting) **little variability** (26,217-27,250); • PSS costs (add 3% to mean incremental cost per patient versus add 10% to mean incremental cost per patient) **little variability** (27,638 – 29,516); • Cost of additional non-PD survival (from halving to doubling non-PD costs) **medium variability** (25,039 – 30,421); • Cost of treating adverse events (from halving to doubling adverse event costs) **large variability** (22906 – 34,688) • quality of life (methods of imputation for missing values) **large variability** (22,512 – 33,816) • drug administration costs (extreme scenarios of drugs administered on single visit to GP (low) versus daily administration in outpatients (high)) **large variability** (24,115 – 40,253). Inclusion of scenario where patients managed in general practice does not seem consistent with SmPC for topotecan stating requirement for specialist management. Bootstrap analyses conducted and reported as scatterplots and summarised as means and 95% CIs.

Table 2 External validity of economic studies

Item/Study	
1. Patient group – are the patients in the study similar to those of interest in	? sub-group of relapsed SCLC patients. MS estimates at approximately 5% of new SCLC cases

England and Wales?	per year (approx 150 p.a.)
2. Health care system/setting – comparability to England and Wales?; comparability of available alternatives?; similar levels of resources?; institutional arrangements comparable?.	✓
3. Treatment – comparability with clinical management?	✓
4. Resource costs - comparability between study and setting/population of interest?	✓ Resource use from multi-centre trial. Unit costs applied for UK – based on published national sources or expert opinion from UK practitioners
Notes: ? means unclear or unknown ✓ means judged item suitable to generalise to England and Wales with or without some re-adjustment. X means factor judged not suitable as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable.	

Appendix 9: Survival modelling methodology

Overall survival

As described in the main body of the text, the survival model adopted for this report was developed using linear regression to estimate the parameters of a linear transformation of the observed Kaplan Meier estimates for overall survival from the RCT by O'Brien and colleagues. Two parametric survival functions were estimated – a Weibull and a log-logistic survival function – which were compared for goodness of fit to the observed survival functions for best supportive care and for oral topotecan plus BSC.

For a Weibull distribution the survival function is given by

$$S(t) = \exp(-\lambda\, t^{\gamma})$$

with scale parameter λ and shape γ. Taking the log of both sides gives

$$\log(S(t)) = -\lambda\, t^{\gamma}$$

Taking the log of both sides again, gives

$$\log(-\log(S(t))) = \log(\lambda) + \gamma \log(t)$$

which is a linear function and can be fit using least squares methods to provide estimates of λ and γ.

Similarly the log-logistic survival function, given by

$$S(t) = \left[1 + \lambda\, t^{\beta}\right]^{-1}$$

can be transformed to the linear function

$$\log\left(\frac{1-S(t)}{S(t)}\right) = \log(\lambda) + \beta \log(t)$$

This can be fit using least squares methods to provide estimates of λ and β.

The following tables report the parameter estimates and measures of goodness of fit for linear regressions, estimated using STATA, for a Weibull and for a log-logistic survival function. In both cases an additional parameter (Treat) was included in the regression – this was a dummy (0,1) variable that indicated whether the observed survival data were for the topotecan and BSC arm (Treat = 1) or the BSC only arm (Treat = 0).

Regression output for the Weibull survival function:

Goodness of fit

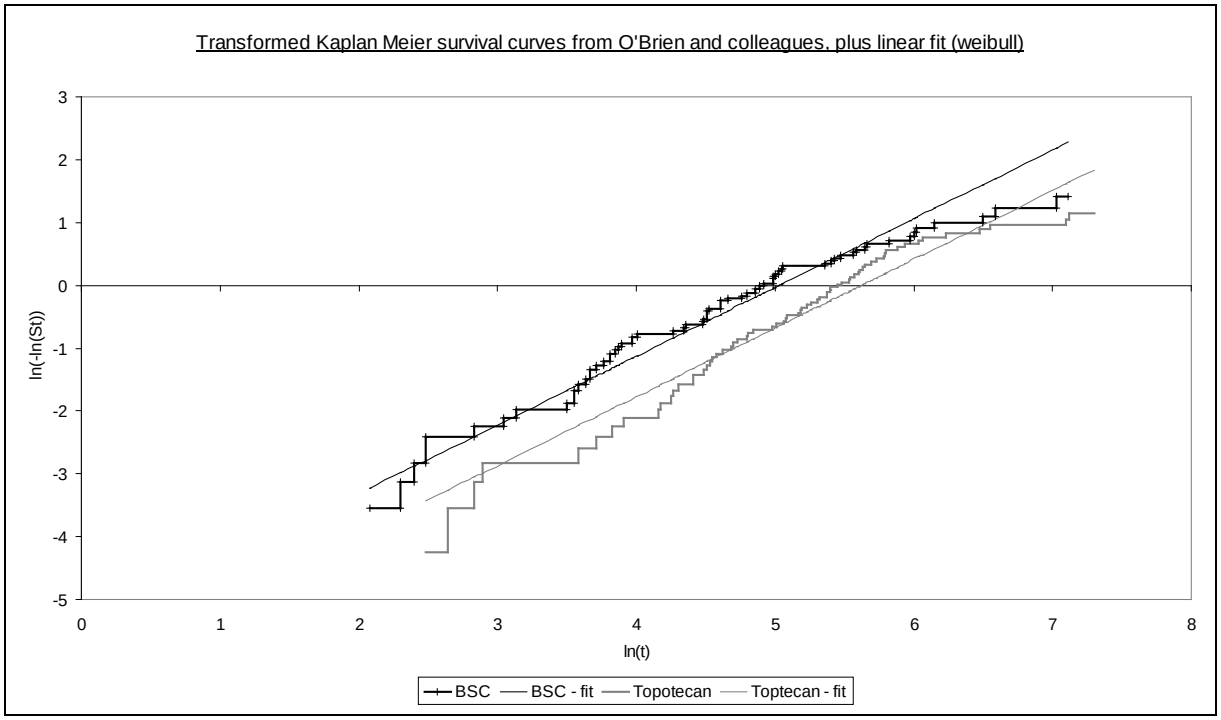
```
      Source |       SS       df       MS              Number of obs =     240
-------------+------------------------------           F(  2,   237) = 2253.43
       Model |  304.815408     2  152.407704           Prob > F      =  0.0000
    Residual |  16.0291723   237  .067633638           R-squared     =  0.9500
-------------+------------------------------           Adj R-squared =  0.9496
       Total |   320.84458   239  1.34244594           Root MSE      =  .26006

------------------------------------------------------------------------------
     weibull |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ln_time |    1.093707   .0163295    66.98   0.000     1.061538    1.125877
       treat |   -.6442615   .0344367   -18.71   0.000    -.7121027   -.5764203
       _cons |   -5.505614   .0792441   -69.48   0.000    -5.661727   -5.349502
------------------------------------------------------------------------------
```

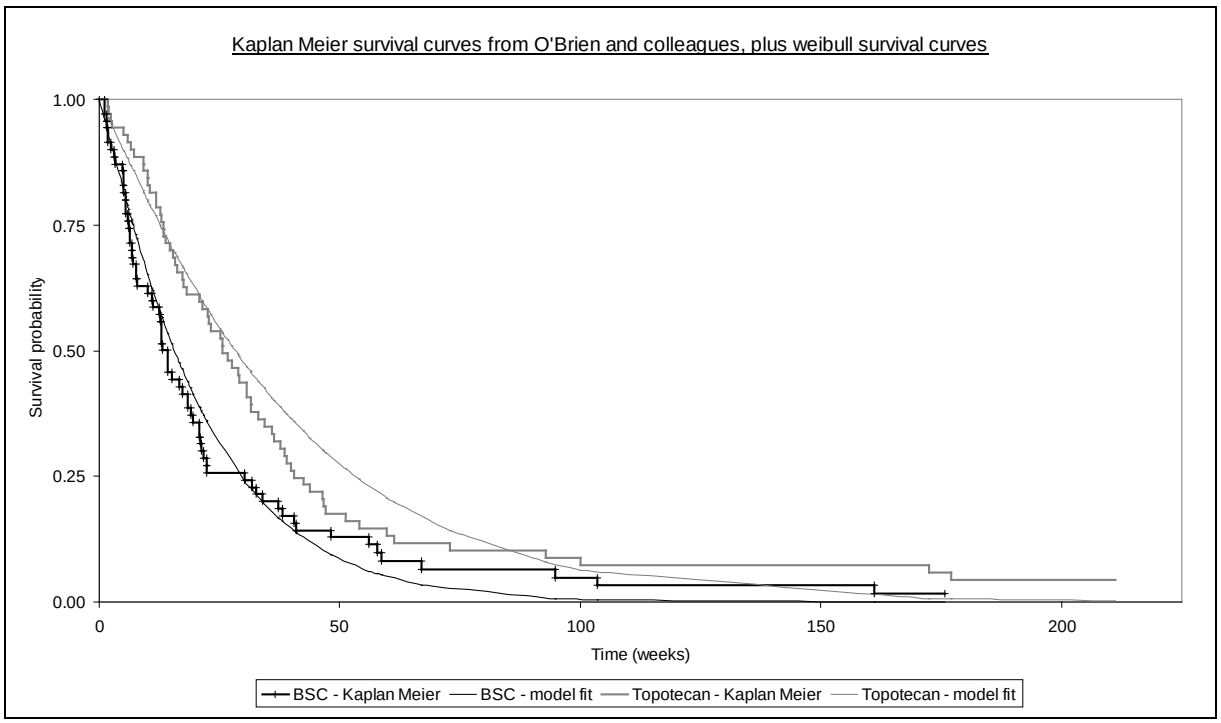
Regression output for the log-logistic survival function:

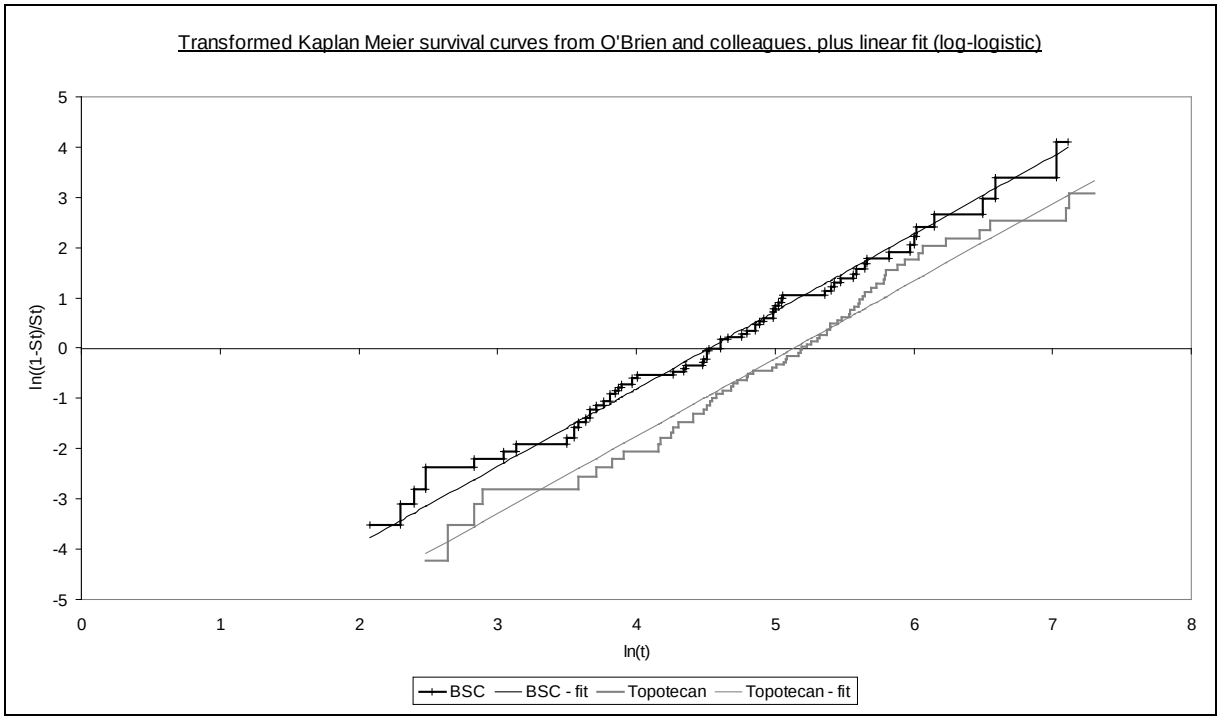
Goodness of fit

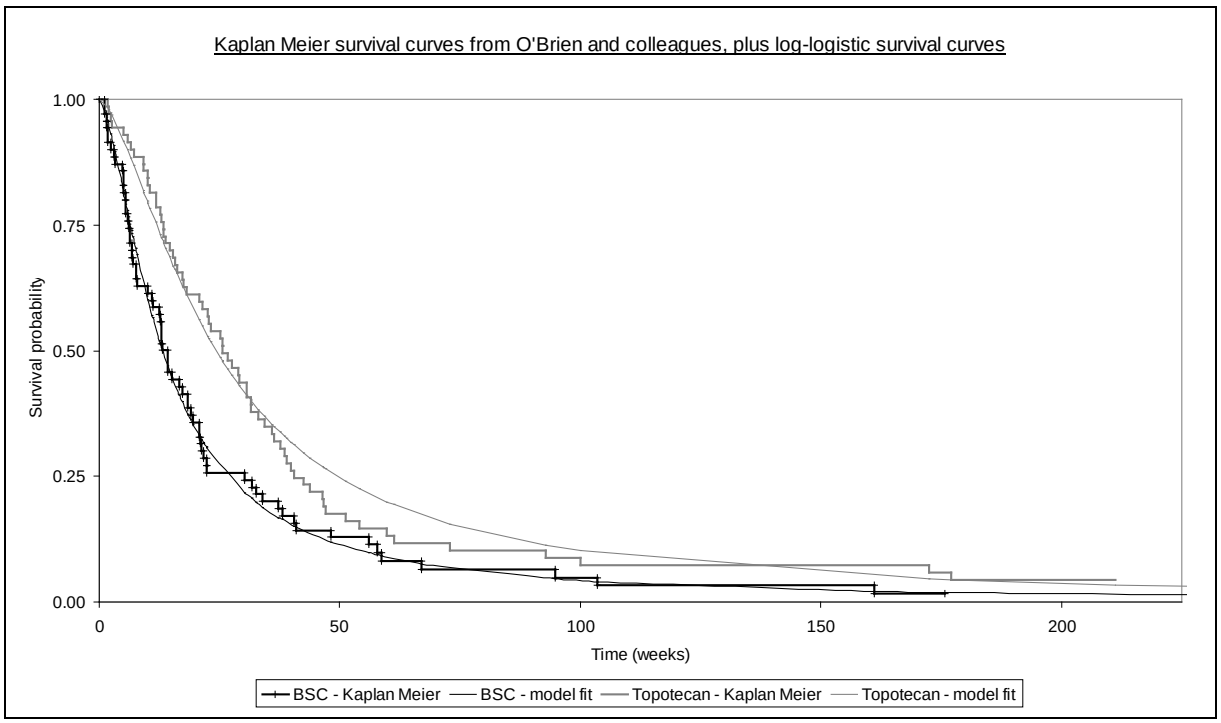
```
      Source |       SS       df       MS              Number of obs =     240
-------------+------------------------------           F(  2,   237) = 5584.19
       Model |  607.177663     2  303.588831           Prob > F      =  0.0000
    Residual |  12.8846967   237  .054365809           R-squared     =  0.9792
-------------+------------------------------           Adj R-squared =  0.9790
       Total |   620.06236   239  2.59440318           Root MSE      =  .23316

------------------------------------------------------------------------------
 logLogistic |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ln_time |    1.542566   .0146404   105.36   0.000     1.513724    1.571408
       treat |   -.9385921   .0308748   -30.40   0.000    -.9994161    -.877768
       _cons |   -6.984087   .0710474   -98.30   0.000    -7.124053   -6.844122
------------------------------------------------------------------------------
```

Both models appear to fit the data well, with the log-logistic having a superior fit. This can be more readily identified by graphing the survival functions. For each parametric survival function we first plot the transformed Kaplan Meier estimates and the fitted linear regressions. In a second figure we show the untransformed Kaplan Meier estimates and the fitted survival functions for oral topotecan and BSC and for BSC alone.


Transformed Kaplan Meier survival curves from O'Brien and colleagues, plus linear fit (weibull)
ln(-ln(St))
ln(t)
BSC
BSC - fit
Topotecan
Toptecan - fit


Kaplan Meier survival curves from O'Brien and colleagues, plus weibull survival curves
Survival probability
Time (weeks)
BSC - Kaplan Meier
BSC - model fit
Topotecan - Kaplan Meier
Topotecan - model fit


Transformed Kaplan Meier survival curves from O'Brien and colleagues, plus linear fit (log-logistic)
ln((1-St)/St)
ln(t)
BSC
BSC - fit
Topotecan
Topotecan - fit


Kaplan Meier survival curves from O'Brien and colleagues, plus log-logistic survival curves
Survival probability
Time (weeks)
BSC - Kaplan Meier
BSC - model fit
Topotecan - Kaplan Meier
Topotecan - model fit

The transformed log-logistic survival functions appear to be closer to linear functions than the transformed Weibull survival functions. The Weibull survival functions are likely to underestimate survival probabilities at higher survival durations when compared with the Kaplan Meier estimates. The modelled probability of survival at 100 weeks is very close to zero, for the Weibull survival function, whereas the Kaplan Meier estimate is around 5%. In contrast the modelled probability of survival at 100 weeks, for the log-logistic survival function, is around 4%.

The interpretation of the parameter coefficient for the dummy variable Treat is more obscure in the log-logistic model, than in the Weibull model where its absolute value can be interpreted as the hazard ratio for oral topotecan and BSC relative to BSC alone for overall survival. This value, 0.644 can be compared directly with the unadjusted hazard ratio of 0.64 and the adjusted hazard ratio of 0.61 reported in the main trial publication by O'Brien and colleagues.[57]

Time to progression

A similar procedure was used to estimate an appropriate function to model the mean time to progression. In this case three potential survival functions were modelled, including an exponential function (in addition to the Weibull and log-logistic survival functions).

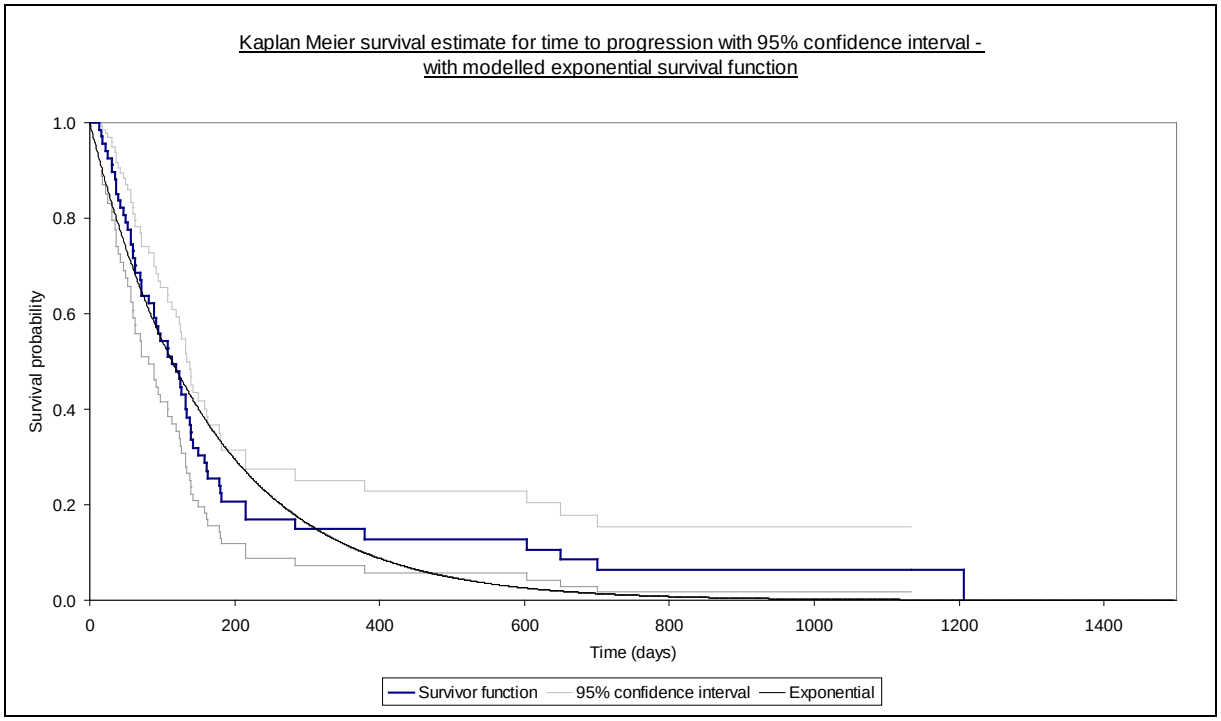
The risk of disease progression was derived from the reported median TTP using an exponential approximation[72]

$$\lambda = -\ln(S)/t$$

where S is the proportion of patients surviving (or in this case without disease progression) at time t. For the median TTP the value of S in the above equation is set, by definition, at 0.5, while t = 16.3 weeks (as presented in section3.1.3.1 of this report). The mean TTP can be calculated by taking the reciprocal of the risk of disease progression ($1/\lambda$). This approach was used in a previous TAR on second-line chemotherapies for advanced ovarian cancer,[69] which included topotecan. The accuracy of the estimate of the mean TTP depends on the adequacy of the exponential approximation, used to convert the median TTP to a risk of disease progression. The appropriateness of this transformation cannot be assessed without reference to the full survival function for time to disease progression, which was not reported in the RCT publication by O'Brien and colleagues.[57] This represents a substantial source of uncertainty in the model.

The economic model submitted with the MS contains participant-level data from the RCT by O'Brien and colleagues, including time to disease progression for patients in the oral topotecan group. The figure below charts the exponential survival function against the Kaplan Meier estimates for time to progression using the patient-level data submitted with manufacturer's economic model. This suggests that the model fits the observed data well up to the median survival. However the fit is much

poorer beyond that point and may significantly underestimate progression free survival, when compared with the Kaplan Meier estimate.



Based on the area under the curve, the estimated mean time to progression using the Kaplan Meier estimates is 30.3 weeks compared to an estimate of 23.52 using the exponential function – underestimating progression free survival by around 48 days. It should be noted that there is considerable uncertainty in the survival functions at longer survival durations, with small numbers of patients included in the analysis above 100 weeks.

To retain compatability with the methods of estimating the overall survival functions, the survival function for disease progression was estimated from linear transformations of the Kaplan Meier estimate of the survival function for time to progression.

Regression output for the Weibull survival function:

Goodness of fit

Source	SS	df	MS	Number of obs	104
Model	129.325342	1	129.325342	F(1, 102)	940.94
Residual	14.0191996	102	.137443133	Prob > F	0.0000
				R-squared	0.9022
Total	143.344542	103	1.39169458	Adj R-squared	0.9012
				Root MSE	.37073

weibull	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ln_time	1.239133	.0403959	30.67	0.000	1.159008	1.319258
_cons	-6.361008	.1872409	-33.97	0.000	-6.732399	-5.989616

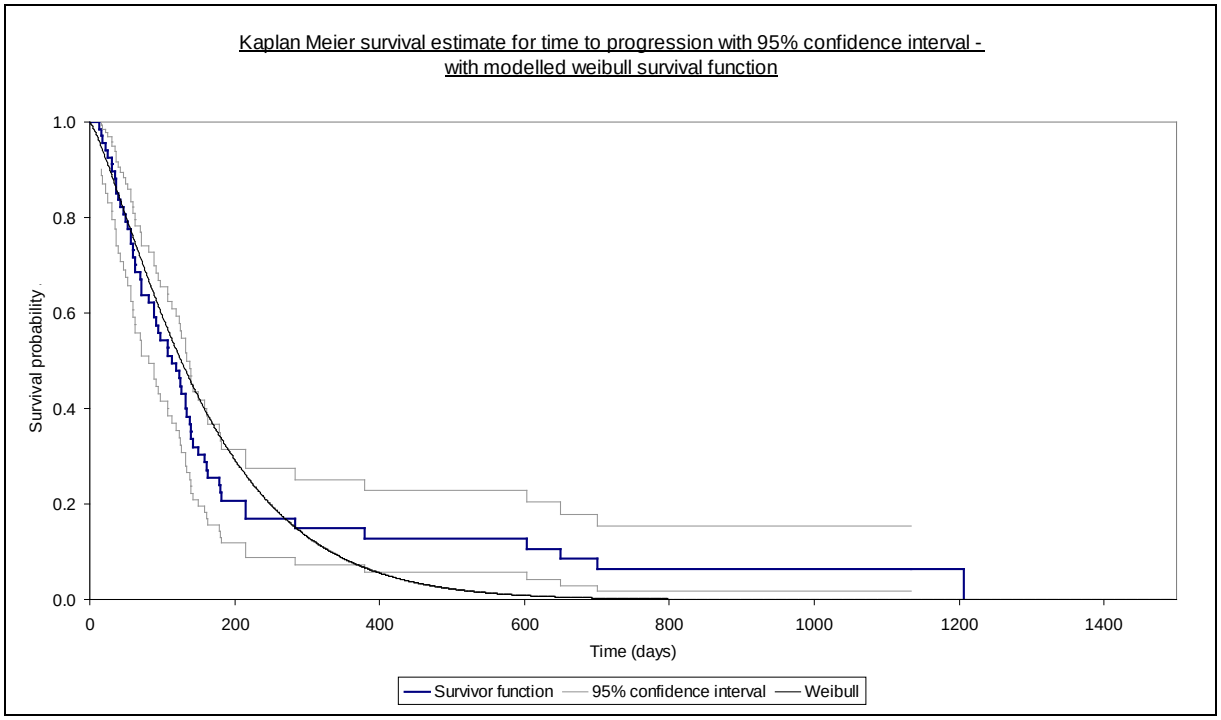
Regression output for the log-logistic survival function:

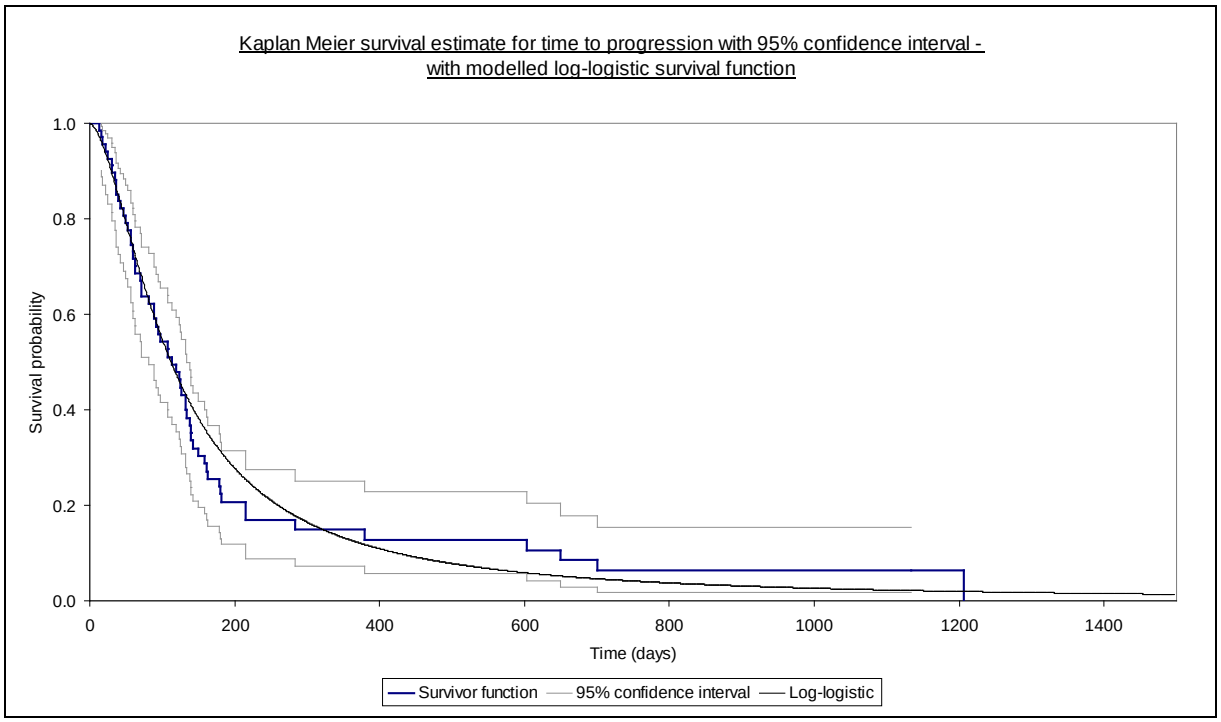
Goodness of fit

Source	SS	df	MS	Number of obs	104
Model	230.206518	1	230.206518	F(1, 102)	2437.28
Residual	9.63412526	102	.094452208	Prob > F	0.0000
				R-squared	0.9598
Total	239.840644	103	2.32854994	Adj R-squared	0.9594
				Root MSE	.30733

logLogistic	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ln_time	1.653237	.0334875	49.37	0.000	1.586814	1.719659
_cons	-7.803979	.1552191	-50.28	0.000	-8.111856	-7.496103

As for overall survival, the modelled survival functions for time to progression were plotted against the Kaplan Meier estimates.





The log-logistic function appears to give a better fit than either the simple exponential approximation, or the regression-based Weibull function. Comparing the mean TTP estimated using each of these functions, we get 22.7 weeks with the Weibull function and 28.5 weeks using the log-logistic function. While the log-logistic survival function clearly fits the observed data better than the alternative functions (Weibull and exponential), all three appear to under-estimate mean TTP compared with the area under the Kaplan Meier curve. However, it should be borne in mind, as noted

above, that there is considerable uncertainty in the survival functions at longer survival durations, as indicated by the wide 95% confidence interval, with the data contributing to estimated progression free survival above 110 weeks being contributed by two patients.

Appendix 10: Input parameters for probabilistic sensitivity analysis

Overall survival

Correlation between parameters in the overall survival regression is handled using the Cholesky decomposition method.[82] The Cholesky decomposition of the variance-covariance matrix for the regression used to fit the log-logistic survival function is shown below:

	ln(t)	Treat	ln(λ)
ln(t)	0.014640	0.000000	0.000000
Treat	-0.006566	0.030169	0.000000
ln(λ)	-0.067545	-0.016090	0.015051

The parameter estimates for the regression are shown below:

ln(t)	Treat	ln(λ)
1.542566	-0.938592	-6.984087

In each simulation three draws are taken from standard normal distributions (mean = 0, standard deviation = 1), labelled here as z_1, z_2, and z_3. Three new variables (Tz_1, Tz_2, and Tz_3) are defined, by multiplying elements of the Cholesky decomposition matrix (C) by the values drawn from standard normal distributions (z_1, z_2, and z_3). Identifying elements of the Cholesky decomposition matrix as C[i,j] where i is the row number and j the column number, then:

$Tz_1 = z_1 * C[1,1]$

$Tz_2 = z_1 * C[2,1] + z_2 * C[2,2]$

$Tz_3 = z_1 * C[3,1] + z_2 * C[3,2] + z_3 * C[3,3]$

For each simulation the sampled values of the parameter estimates are therefore defined as:

Tz_1 + ln(t)

Tz_2 + Treat

Tz_3 + ln(λ)

The same approach was used to handle correlation between parameters in the model used to estimate time to progression for patients in the oral topotecan cohort.

Probability of adverse events

The probability of adverse events is based on the number of patients experiencing each grade of adverse event, as reported in the CSR for study 487 (included as Appendix 5 of the MS). These are sampled using the procedure outlined in Briggs and colleagues[82] for sampling from a Dirichlet distribution. Variables x_0, x_1, … x_4 (corresponding to grades 0 through 4 for a given toxicity) are drawn from independent gamma distributions with shape parameters α_0, α_1, ... α_4 (corresponding to the count of patients experiencing the given grades of toxicity) and a common scale parameter of 1.

Thus the simulated count for each grade (j) of a given toxicity is $x_j \sim Gamma(\alpha_j, 1)$

The simulated proportion is calculated by dividing the simulated count for each grade by the sum of the simulated counts for all grades of the relevant toxicity $\frac{x_j}{\sum_{j=0}^{4} x_j}$

Health state utility

The rate of deterioration in QoL per three month interval for oral topotecan and BSC and for BSC is sampled across the 95% confidence interval reported by O'Brien and colleagues[57] see table below:

Cohort	Point estimate	LCI	UCI	Standard error	Distribution
Topotecan + BSC	-0.05	-0.11	0.02	0.03827	Normal
BSC	-0.20	-0.27	-0.12	0.03316	Normal

Chemotherapy courses and body surface area

The mean (and standard error) for the number of courses of oral topotecan and patients' body surface area were estimated from data included in the manufacturer's economic model. These were simulated using normal distributions.

Variable	Mean	Standard error	Distribution
Number of courses per patient	3.9296	0.2649	Normal
Body surface area	1.8404	0.0240	Normal

Costs

Costs included in the PSA were those related to outpatient provision of chemotherapy, general medical management in outpatients, inpatient and outpatient management of adverse events and palliative care costs. Drug costs were not sampled during the PSA, but were included at values quoted in the BNF.

Costs derived from NHS Reference Costs were sampled using estimated "standard errors". These assumed that a variation of plus or minus 25% was an appropriate confidence interval for the average reference costs. The estimated standard errors are shown in column 3 of the table below. Parameters for gamma distributions (shown in columns labelled Alpha and Beta) were derived using the "method of moments"[82] based on the means and estimated "standard errors". The simulated values were inflated to 2007/08 prices using appropriate inflation indices, as for the base case and deterministic sensitivity analyses.

The estimated standard error for palliative care costs was derived using the minimum and maximum values presented by Oliver and colleagues,[49] as these were the only summary data for the distribution of palliative care costs reported.

Item	Mean	"Standard error"	Alpha	Beta	Distribution
Oral topotecan (per mg)	30.00				
IV topotecan (per ?)	0.00				
Outpatient attendance for oral chemotherapy	178.99	15.94	126.07	1.4	Gamma
Full blood count	2.90				
U&E	4.70				
LFT	4.70				
Chest X ray	27.71	2.47	126.07	0.2	Gamma
Day case admission	355.43	31.66	126.07	2.8	Gamma
Inpatient elective excess bed day	241.76	21.53	126.07	1.9	Gamma
Inpatient non-elective excess bed day	181.73	16.18	126.07	1.4	Gamma
Outpatient attendance	200.78	17.88	126.07	1.5	Gamma
Intensive care (per day)	989.82	88.15	126.07	7.8	Gamma
GP visit	36.00				
Cost of palliative care (per patient)	3495.00	1,168.46	8.95	390.643	Gamma
Antibody Screen	10.40				
Electronic cross-match	25.00				
Serological cross-match	30.90				
Standard red cells (per unit)	133.90				
Platelets (per unit)	208.46				
Blood transfusion (per transfusion)	78.80				
Platelets transfusion (per transfusion)	705.00				

Appendix 11: Estimating QALY weights over time (from published values)

O'Brien and colleagues[57] and Chen and colleagues[64] briefly reported on a pooled analysis of utility data, collected using the EQ-5D and valued using a population tariff, using a mixed model (to account for the inclusion of repeated observations for trial participants). The CSR for Study SK&F-104864/478, submitted to NICE as Appendix 5 of the manufacturer's submission, contains slightly more detail on the methods used. The CSR makes clear that the analysis has used EQ-5D utility scores, derived using responses from patients in the RCT by O'Brien and colleagues[57] and valued using the tariff reported by Dolan and colleagues.[80] The EQ-5D was administered at baseline and at each clinic visit (every three weeks) – missing data for the EQ-5D are not reported or discussed in the main trial publication (O'Brien and colleagues[57]) or the CSR. The CSR reports that the mixed model was estimated using restricted maximum likelihood and included treatment, baseline EQ-5D utility, time and a treatment by time interaction as fixed covariates. The random effects were intercept and time, while course of therapy was included as a repeated effect. An unstructured covariance structure was used for the random effects and a spatial covariance structure for the repeated effect. No further detail of this analysis is provided in the CSR.

Both O'Brien and colleagues[57] and Chen and colleagues[64] state that the "rate of deterioration" in utility was -0.05 per three month period for oral topotecan and BSC and was -0.20 per three month period for BSC. We interpreted this to indicate that, for each three month period, the mean utility reduces from baseline by 5% for the oral topotecan and BSC cohort and by 20% for the cohort receiving BSC alone.

Assuming a baseline utility for patients in both cohorts of 0.70, based on the reported baseline utility of patients in the RCT by O'Brien and colleagues who contributed data to the pooled analysis (0.72 for oral topotecan and BSC and 0.68 for BSC) we estimated mean utility over time for each arm over a period of 12 months as:

Time (months)	Oral topotecan and BSC	BSC
0	0.7000	0.7000
3	0.6650	0.5600
6	0.6318	0.4480
9	0.6002	0.3584
12	0.5702	0.2867

To estimate a daily rate of deterioration in utility we subtracted the natural log of the baseline utility from the natural log of the value at three months, for each arm:

-0.4080 - -0.3567 = -0.0513 (for oral topotecan and BSC) and

-0.5798 - -0.3567 = -0.2231 (for BSC).

Dividing these values by the mean number of days in three months (91.3125) gives -0.000562 for oral topotecan and BSC and -0.002444 for BSC. To estimate the utility at a given number of days from baseline simply enter the appropriate values in the following formula:

-0.3567 + UtilityDecrement x days

(where -0.3567 is the natural log of 0.7, the assumed baseline utility value) and exponentiate the result. For example to calculate the utility value for oral topotecan and BSC and for BSC at one year:

exp(ln(0.7)+-0.000562*(365.25)) = 0.5702 (for oral topotecan and BSC) and

exp(ln(0.7)+-0.002444*(365.25)) = 0.2867 (for BSC).

Appendix 12: Detailed calculation of adverse event costs

Detailed assumptions for resource use with haematological toxicity

Toxicity	Grade	Resource Use	Resource use assumption
Neutropenia	3	Out-patient visit Amoxycillin	Single attendance by 50% of affected patients Oral capsule, non-proprietary. Dosage 500mg every 8 hours. Up to seven days.
	4	Inpatient admission Piperacillin Saline	All affected patients admitted – average stay of 3.5 days (range 2 – 5 days) Intravenous. 4.5g every 6 hours for duration of stay (14 for average stay of 3.5 days) 20ml for dilution of Tazocin + 100ml for IV infusion of Piperacillin
Thrombocytopenia	3	No treatment	
	4	Day case admission Platelet transfusion Type and cross	Single attendance for all affected patients
Anaemia	3	Day case admission Blood transfusion Type and cross	Single attendance for all affected patients
	4	Day case admission Blood transfusion Type and cross	Single attendance for all affected patients
Sepsis		Inpatient admission Piperacillin Clarithromycin Saline Fluconazole IV	Total stay 10 days, average of 5 (range 3 to 7) ward days and 5 (range 3 to 7) in ICU days Intravenous. 4.5g every 6 hours for five days (14 for average stay of 3.5 days) 500mg, twice daily for 10 days 20ml for dilution of Tazocin + 100ml for IV infusion of Piperacillin Intravenous, non-proprietary. 100-mL at 2mg/mL, 1 per day for seven days

Table A9.2 Detailed unit cost assumptions for resource use associated with haematological toxicity

Toxicity	Grade	Resource Use	Resource use assumption	Unit Cost (£)	Unit measure
Neutropenia	3	Out-patient visit	General Medicine (specialty code 300). Consultant Led First Attendance Outpatient Face to Face. Worksheet "TCLFASFF"	207.48	per visit
		Amoxycillin	21 x 500mg capsules (Non-proprietary) = £1.37.	0.065	per capsule
	4	Inpatient admission	Respiratory Neoplasms with Major CC (DZ17A). Excess bed day cost. Worksheet "TEIXS"	249.83	per day
		Tazocin	4.5 g powder for reconstitution	15.79	per infusion
		Saline	Main and colleagues[69], page 96	0.06	per ml
Thrombocytopenia	3	No treatment			
	4	Day case admission	Respiratory Neoplasms with Major CC (DZ17A). Worksheet "TDC"	367.29	per admission
		Platelet transfusion	Main and colleagues[69]	805.67	per transfusion
		Type and cross	Southampton University Hospitals Trust	36.88	per transfusion
Anaemia	3	Day case admission	Respiratory Neoplasms with Major CC (DZ17A). Worksheet "TDC"	367.29	per admission
		Blood transfusion	Main and colleagues[69]	90.05	per transfusion
		Type and cross	Southampton University Hospitals Trust	36.88	per transfusion
	4	Day case admission	Respiratory Neoplasms with Major CC (DZ17A). Worksheet "TDC"	367.29	per admission
		Blood transfusion	4 units red blood cells (expert advice)	133.90	per unit
		Type and cross	Southampton University Hospitals Trust	36.88	per transfusion
Sepsis		Inpatient admission			
		ICU	Intensive Therapy Unit / Intensive Care Unit: 1 Organ Supported (XC06ZTHE). Worksheet "TCCSAL"	1,022.86	per day
		Ward	Respiratory Neoplasms with Major CC (DZ17A). Excess bed day cost. Worksheet "TEIXS	249.83	per day
		Tazocin	4.5 g powder for reconstitution	15.79	per infusion
		Clarithromycin	pack of 14 x 500mg tablets = £7.47	0.535	per tablet
		Saline	Main and colleagues[69]	0.06	per ml
		Fluconazole IV	100-mL bottle at 2mg/mL = £29.28	29.28	per infusion

Table A9.3 Detailed assumptions for resource use with non-haematological toxicity

Toxicity	Grade	Resource Use	Resource use assumption
Diarrhoea	2	Outpatient visit Loperamide	Single attendance by all affected patients Oral tablet. 16 mg per day for 5 days
	3	Inpatient admission Loperamide Buscopan Codeine phosphate	All affected patients admitted – average stay of 5 days Oral tablet. 16 mg per day for 7 days. Oral tablet. 20 mg, four times per day for 7 days Oral tablet, non-proprietary. 30mg four times per day for 7 days
	4	Inpatient admission Loperamide Buscopan Ciprofloxacin IV Metronidazole IV Codeine	All affected patients admitted – average stay of 5 days Oral tablet. 16 mg per day for 7 days. Oral tablet. 20 mg, four times per day for 7 days 400mg twice daily, for two days. As 2mg/mL in 200mL bottle. 500mg, up to four times. As 5mg/mL in 100mL container. Oral tablet, non-proprietary. 30mg four times per day for 7 days
Nausea/vomiting	3	Outpatient visit Dexamethasone Granisetron	Single attendance for all affected patients Oral tablet. 8 mg, twice daily for 10 days. Oral tablet. 2mg daily for 10 days.
	4	Inpatient admission Dexamethasone IV Granisetron IV Saline Cyclizine	All affected patients admitted – average stay of 5 days 20mg single dose 3mg, three times over 24 hours 15 ml for dilution of Granisetron 50mg, three times daily for 5 days

Table A9.4 Detailed unit cost assumptions for resource use associated with non-haematological toxicity

Toxicity	Grade	Resource Use	Resource use assumption	Unit Cost (£)	Unit measure
Diarrhoea	2	Outpatient visit	General Medicine (specialty code 300). Consultant Led First Attendance Outpatient Face to Face. Worksheet "TCLFASFF"	207.48	per visit
		Loperamide	pack of 30 x 2mg tablets = £2.15	0.07	per tablet
	3	Inpatient admission	Respiratory Neoplasms with Major CC (DZ17A). Excess bed day cost. Worksheet "TEIXS"	249.83	per day
		Loperamide	pack of 30 x 2mg tablets = £2.15	0.07	per tablet
		Buscopan	pack of 56 x 10mg tablets = £2.59	0.05	per tablet
		Codeine phosphate	28 x 30mg tablets = £0.97	0.035	per tablet
	4	Inpatient admission	Respiratory Neoplasms with Major CC (DZ17A). Excess bed day cost. Worksheet "TEIXS"	249.83	per day
		Loperamide	pack of 30 x 2mg tablets = £2.15	0.07	per tablet
		Buscopan	pack of 56 x 10mg tablets = £2.59	0.05	per tablet
		Codeine phosphate	28 x 30mg tablets = £0.97	0.035	per tablet
		Ciprofloxacin IV	200-mL bottle at 2mg/mL = £22.00	22.00	per infusion
		Metronidazole IV	100-mL container at 5mg/mL = £3.41	3.41	per infusion
Nausea/vomiting	3	Outpatient visit	General Medicine (specialty code 300). Consultant Led First Attendance Outpatient Face to Face. Worksheet "TCLFASFF"	207.48	per visit
		Dexamethasone	20 x 2mg tablets = £3.27	0.165	per tablet
		Granisetron	5 x 2mg tablets = £65.49	13.10	per tablet
	4	Inpatient admission	Respiratory Neoplasms with Major CC (DZ17A). Excess bed day cost. Worksheet "TEIXS"	249.83	per day
		Dexamethasone IV	1-mL amp at 4mg/mL = £1.00	5.00	per infusion
		Granisetron IV	3-mL amp at 1mg/mL = 25.79	25.79	per infusion
		Saline	Main and colleagues[69]	0.06	per ml
		Cyclizine	20 x 50mg tablets = £1.48	0.075	per tablet

Appendix 13: Questions to clinician experts – management of patients treated with topotecan (oral or intravenous) and management of treatment-related toxicity

Specific questions regarding the management of patients being treated with topotecan (in oral or intravenous form) are listed below:

- **What tests would be required prior to starting treatment with topotecan.** Assume that a full blood count is required since the SmPC states that "prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of ≥ 9 g/dl (after transfusion if necessary)".
    - Would any other tests be required prior to starting treatment with topotecan?
- **What tests would be used to monitor patients receiving chemotherapy with topotecan**. Assume haematological toxicity is assessed by full blood count.
    - Would this be assessed only at start of each treatment cycle or would this happen more frequently?
    - Would assessment/ frequency of assessment for haematological toxicity differ between oral versus IV topotecan?
    - What tests would be routinely requested for assessing other toxicities? Please specify types of test, the frequency of testing and toxicities being assessed.
    - Would patients receiving oral topotecan have additional monitoring in primary care (for example, visits by district nurses)? How frequently would patients receiving oral topotecan attend for treatment or monitoring during each treatment cycle?
- **Would patients attending for topotecan be required to take any premedications or concomitant medication?**
    - Would patients require premedication prior to topotecan by intravenous infusion?
    - Would patients require premedication prior to oral topotecan?
    - Would patients require concomitant medication with topotecan by intravenous infusion?
    - Would patients require concomitant medication with oral topotecan?
    - The trial report by O'Brien and colleagues specifically refers to a proportion (3%) of patients receiving granulocyte colony-stimulating factor – would this be prescribed as prophylaxis against neutropenia?
    - The trial report by O'Brien and colleagues specifically refers to a proportion of patients (3%) receiving erythropoietin – would this be prescribed as prophylaxis?
- **Topotecan for intravenous infusion is supplied as powder for reconstitution**. SmPC states "saline (0.9 % w/v sodium chloride intravenous infusion or 5 % w/v glucose intravenous infusion) is required for reconstitution of powder to a final concentration of between 25 and 50 microgram/ml".
    - Can you indicate the quantity of saline required to achieve this concentration for a patient requiring a dose of 2.7mg per day (i.e. dosage of 1.5mg/m^2 per day for patient with body surface area of 1.8m^2)?

- **Dose escalation/ dose reduction**
    - If a patient has their chemotherapy dose increased, due to lack of efficacy, in one cycle does the dose remain at the escalated level for their remaining cycles of treatment on a given agent?
    - If a patient has their chemotherapy dose reduced, due to toxicity, in one cycle does the dose remain at the reduced level for their remaining cycles of treatment on a given agent?

- **If the exact dosage of oral topotecan is not available would you recommend rounding the dosage up or down?** For example, the exact dosage for a patient with body surface area of 1.8m^2 would be 4.14mg per day, at a dosing schedule of 2.3mg/m^2 per day. With oral topotecan available in 1mg and 0.25mg capsules would you recommend rounding up to 4.25mg per day or rounding down to 4.00mg per day?

Treatment of toxicity/ adverse events: a previous review conducted for NICE (Main and colleagues, HTA 2006; 10(9)), which included topotecan, reported estimates of the costs of managing treatment-related toxicity. While the review was concerned with the use of topotecan for treatment of advanced ovarian cancer, we are aware that the dosage, frequency of administration and cycle length are the same for advanced ovarian cancer and for small cell lung carcinoma. **Would it be reasonable to adopt similar assumptions for managing (topotecan) treatment-related toxicity in relapsed small cell lung cancer patients as for advanced ovarian cancer patients?** The assumptions and costs adopted in the advanced ovarian cancer review (which were derived from one of the manufacturers' submissions to the NICE appraisal) are listed below. First we list the assumptions with regard to how patients are managed – as out-patient, day case or inpatient – and secondly the assumptions regarding drug treatment or specific interventions (such as transfusions) provided.

Table 1 - management of haematological toxicity

Toxicity/ adverse event	Grade	Managed as	Length of stay
Neutropenia	3	Out-patient	Single attendance by 50% of affected patients
	4	Inpatient	3.5 days (range 2 to 5 days)
Thrombocytopaenia	3	No treatment	
	4	Day case	All patients attend for platelet transfusion
Anaemia	3	Day case	Single attendance for all affected patients
	4	Day case	Single attendance for all affected patients
Sepsis	3	Inpatient	Average 4.5 days (range 3 to 6 days)
	4	Inpatient	Total stay of 10 days on average, with an average of 5 days (range 3 to 7 days) in ICU and 5 days (range 3 to 7 days) on the ward.

No assumptions were listed for febrile neutropenia – **would it be reasonable to regard these as a subset of Grade 4 neutropenia and apply the same management assumptions**?

Table 2 - management of non-haematological toxicity

Toxicity/ adverse event	Grade	Managed as	Length of stay
Diarrhoea	3	Inpatient	5 days
	4	Inpatient	5 days
Vomiting	3	Outpatient	Single attendance for all affected patients
	4	Inpatient	5 days

Table 3 - drug treatment or specific interventions for haematological toxicity

Toxicity/ adverse event	Grade	Drug/ intervention	Quantity (total cost)
Neutropenia	3	Ciprofloxacin	6 (£1.50)
	4	Ciprofloxacin G-CSF	6 (£1.50) 5 (£77.03)
Thrombocytopaenia	3	No treatment	
	4	Platelet transfusion Type and cross	1 (£78.80) 1 (£18.00)
Anaemia	3	Platelet transfusion Type and cross	1 (£78.80) 1 (£18.00)
	4	Platelet transfusion Type and cross	1 (£78.80) 1 (£18.00)
Sepsis	3	Gentamicin	1 (£61.25)

		Tazocin	1	(£368.48)
	4	Gentamicin	1	(£61.25)
		Tazocin	1	(£368.48)
		Saline	1	(£42.00)
		Fluconzole IV	1	(£204.96)

Table 4 - drug treatment or specific interventions non-haematological toxicity

Toxicity/ adverse event	Grade	Drug/ intervention	Quantity (total cost)	
Diarrhoea	3	Buscopan	1	(£1.39)
		Ciprofloxacin	6	(£1.50)
		Codine	1	(£0.33)
		Loperamide	2.5	(£0.08)
	4	Buscopan	1	(£1.39)
		Ciprofloxacin	6	(£1.50)
		Codine	1	(£0.33)
		Loperamide	2.5	(£0.08)
Vomiting	3	Dexamethasone	6	(£0.51)
		Granisetron	1	(£383.95)
	4	Saline	1	(£42.00)
		Dexamethasone IV	1	(£6.60)
		Granisetron IV	1	(£360.00)
		Cyclizine	1	(£8.55)

Appendix 14: Relative risks of adverse events - IV versus oral topotecan.

Haematological adverse events

Neutropenia		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 3	Eckardt	0.9035	0.2019	0.6083	1.3420	75.2%
	von Pawel	1.2483	0.3514	0.6269	2.4856	24.8%
	Pooled	0.9789	0.1750	0.6946	1.3796	
Grade 4	Eckardt	1.3663	0.1065	1.1089	1.6835	80.0%
	von Pawel	1.9071	0.2128	1.2567	2.8941	20.0%
	Pooled	1.4607	0.0952	1.2119	1.7605	

Thrombocytopenia		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 3	Eckardt	1.2667	0.2152	0.8308	1.9313	71.4%
	von Pawel	0.9623	0.3397	0.4945	1.8725	28.6%
	Pooled	1.1708	0.1818	0.8198	1.6719	
Grade 4	Eckardt	0.6279	0.2167	0.4106	0.9602	70.1%
	von Pawel	0.8935	0.3315	0.4666	1.7110	29.9%
	Pooled	0.6979	0.1814	0.4891	0.9958	

Anaemia		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 3	Eckardt	1.6154	0.2212	1.0471	2.4922	62.9%
	von Pawel	1.3747	0.2880	0.7817	2.4174	37.1%
	Pooled	1.5215	0.1754	1.0788	2.1459	
Grade 4	Eckardt	0.5000	0.6014	0.1538	1.6251	72.7%
	von Pawel	0.9623	0.9806	0.1408	6.5760	27.3%
	Pooled	0.5980	0.5127	0.2189	1.6333	

Non-haematological adverse events

Diarrhoea		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 2	Eckardt	0.3524	0.3942	0.1627	0.7631	87.91%
	von Pawel	0.1606	1.0628	0.0200	1.2896	12.09%
	Pooled	0.3205	0.3696	0.1553	0.6613	
Grade 3	Eckardt	0.1689	0.7552	0.0384	0.7418	67.10%
	von Pawel	0.1927	1.0784	0.0233	1.5954	32.90%
	Pooled	0.1764	0.6186	0.0525	0.5929	
Grade 4	Eckardt	1.0132	0.9934	0.1446	7.1006	66.54%
	von Pawel	0.9636	1.4011	0.0618	15.0138	33.46%
	Pooled	0.9963	0.8104	0.2035	4.8776	

Nausea		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 3	Eckardt	0.5789	0.6163	0.1730	1.9373	62.38%
	von Pawel	0.9636	0.7935	0.2035	4.5638	37.62%
	Pooled	0.7013	0.4867	0.2701	1.8205	
Grade 4	Eckardt	2.0263	1.2194	0.1857	22.1136	56.90%
	von Pawel	0.9636	1.4011	0.0618	15.0138	43.10%
	Pooled	1.4709	0.9198	0.2425	8.9232	

Vomiting		RR	SE(lnRR)	95% CI Lower	95% CI Upper	Weight
Grade 3	Eckardt	0.6079	0.7213	0.1479	2.4992	45.77%
	von Pawel	0.4130	0.6627	0.1127	1.5136	54.23%
	Pooled	0.4929	0.4880	0.1894	1.2828	
Grade 4	Eckardt	1.0132	0.9934	0.1446	7.1006	66.54%
	von Pawel	0.9636	1.4011	0.0618	15.0138	33.46%
	Pooled	0.9963	0.8104	0.2035	4.8776	

Appendix 15: Estimating relative time to progression for IV topotecan versus oral topotecan

Plots of the Kaplan Meier estimates of time to progression for patients treated with oral topotecan or IV topotecan in the RCTs reported by von Pawel and colleagues[58] and Eckardt and colleagues[56] were scanned using TechDig software and then imported into Microsoft Excel. These were transformed, as described in Appendix 9, to be fit using least squares methods and the data were analysed using STATA 9.

A log-logistic survival function for time to progression was estimated, as for oral topotecan (described in Appendix 9), with the addition of a dummy (0,1) variable to indicate whether the data were for the oral topotecan arm (IV_Topo=0) or the IV topotecan arm (IV_Topo=1).

Regression output for log-logistic survival function for time to progression in the RCT reported by von Pawel and colleagues:[58]

```
      Source |       SS       df       MS              Number of obs =     118
-------------+------------------------------           F(  2,   115) = 1117.30
       Model |  352.437589     2  176.218795           Prob > F      =  0.0000
    Residual |  18.1375774   115  .157718064           R-squared     =  0.9511
-------------+------------------------------           Adj R-squared =  0.9502
       Total |  370.575167   117  3.16730912           Root MSE      =  .39714

------------------------------------------------------------------------------
 logLogistic |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ln_time |    2.00121   .0423367    47.27   0.000     1.917349    2.085071
     IV_Topo |   .2709251     .07345     3.69   0.000     .1254348    .4164153
       _cons |  -5.217638    .125721   -41.50   0.000    -5.466667   -4.968609
------------------------------------------------------------------------------
```

Regression output for log-logistic survival function for time to progression in the RCT reported by Eckardt and colleagues:[56]

```
      Source |       SS       df       MS              Number of obs =     148
-------------+------------------------------           F(  2,   145) = 1848.82
       Model |  435.650575     2  217.825288           Prob > F      =  0.0000
    Residual |  17.0837308   145  .117818833           R-squared     =  0.9623
-------------+------------------------------           Adj R-squared =  0.9617
       Total |  452.734306   147  3.07982521           Root MSE      =  .34325

------------------------------------------------------------------------------
 logLogistic |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ln_time |   1.812713   .0298959    60.63   0.000     1.753625    1.871801
     IV_Topo |  -.2290531   .0587501    -3.90   0.000    -.3451704   -.1129359
       _cons |  -4.810578   .0955714   -50.33   0.000    -4.999472   -4.621685
------------------------------------------------------------------------------
```

The coefficient for the dummy variable, IV_Topo, has opposite signs in the two regressions – as would be expected since the two trials gave inconsistent results in terms of the relative time to progression with IV and oral formulations of topotecan. In the RCT reported by von Pawel and colleagues[58] median TTP was shorter for IV topotecan (13 weeks compared with 15 weeks for IV and

oral topotecan, respectively), whereas in the RCT reported by Eckardt and colleagues[56] median TTP was longer for IV topotecan (14.6 weeks compared with 11.9 weeks for IV and oral topotecan, respectively). Median TTP for oral topotecan in both trials is shorter than that reported in the RCT by O'Brien and colleagues,[57] where median TTP for oral topotecan was 16.3 weeks.

IV_Topo was included as an additional covariate in the regression model estimated for time to progression (described in Appendix 9), taking values estimated in the regressions above, to estimate the time to disease progression for patients included in the model for oral topotecan, if they were treated with IV topotecan. This variable only effects the duration of, post-treatment, non-progressive disease survival. Estimated median time to progression using the model is reported in Table below.

Table

	Median TTP (weeks)	Mean TTP (weeks)
Oral topotecan	16.03	28.30
IV topotecan (based on von Pawel and colleagues[58])	13.61	24.37
IV topotecan (based on Eckardt and colleagues[56])	18.41	32.07