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National Institute for Health Research

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Abstract

Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation

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Background: The National Institute for Health and Care Excellence (NICE) has issued multiple guidance for the first-line management of patients with lung cancer and recommends different combinations of chemotherapy treatments. This review provides a synthesis of clinical effectiveness and cost-effectiveness evidence supporting current guidance.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

Data sources: Three electronic databases (MEDLINE, EMBASE and The Cochrane Library) were searched from 2001 to August 2010.

Review methods: Trials that compared first-line chemotherapy currently licensed in Europe and recommended by NICE in chemotherapy-naive adult patients with locally advanced or metastatic NSCLC were included. Data on key outcomes including, but not limited to, overall survival (OS), progression-free survival (PFS) and adverse events (AEs) were extracted. For the assessment of cost-effectiveness, outcomes included incremental cost per quality-adjusted life-year (QALY) gained. Analyses were performed for three NSCLC subpopulations: patients with predominantly squamous disease, patients with predominantly non-squamous disease and patients with epidermal growth factor receptor (EGFR) mutation-positive (M+) status. Meta-analysis and mixed-treatment comparison methodology were conducted where appropriate.

Results: Twenty-three trials involving >11,000 patients in total met the inclusion criteria. The quality of the trials was poor. In the case of patients with squamous disease, there were no statistically significant differences in OS between treatment regimes. The mixed-treatment comparison demonstrated that, in patients with non-squamous disease, pemetrexed (Alimta®, Eli Lilly and Company; PEM) + platinum (PLAT) increases OS statistically significantly compared with gemcitabine (Gemzar®, Eli Lilly and Company; GEM) + PLAT [hazard ratio (HR) = 0.85; 95% confidence interval (CI) 0.74 to 0.98] and that docetaxel (Taxotere®, Sanofi-aventis; DOC) + PLAT increases OS statistically significantly compared with paclitaxel (Abraxane®, Celgene Corporation; PAX) + PLAT (HR = 0.79, 95% CI 0.66 to 0.93). None of the comparisons

found any statistically significant differences in OS among patients with EGFR M+ status. Direct meta-analysis showed a statistically significant improvement in PFS with gefitinib (Iressa®, AstraZeneca; GEF) compared with DOC + PLAT and PAX + PLAT (HR = 0.49; 95% CI 0.33 to 0.73; and HR = 0.38; 95% CI 0.24 to 0.60, respectively).

No papers related to UK decision-making were identified. A de novo economic model was developed. Using list prices (*British National Formulary*), cisplatin (CIS) doublets are preferable to carboplatin doublets, but this is reversed if electronic market information tool prices are used, in which case drug administration costs then become more important than drug acquisition costs. For patients with both squamous and non-squamous disease, moving from low to moderate willingness-to-pay thresholds, the preferred drugs are PAX → GEM → DOC. However, in patients with non-squamous disease, PEM + CIS resulted in increased OS and would be considered cost-effective up to £35,000 per QALY gained. For patients with EGFR M+, use of GEF compared with PAX or DOC yields very high incremental cost-effectiveness ratios. Vinorelbine (Navelbine®, Pierre Fabre Pharmaceutical Inc.) was not shown to be cost-effective in any comparison.

Limitations: Poor trial quality and a lack of evidence for all drug comparisons complicated and limited the data analysis. Outcomes and adverse effects are not consistently combined across the trials. Few trials reported quality-of-life data despite their relevance to patients and clinicians.

Conclusions: The results of this comprehensive review are unique to NSCLC and will assist clinicians to make decisions regarding the treatment of patients with advanced NSCLC. The design of future lung cancer trials needs to reflect the influence of factors such as histology, genetics and the new prognostic biomarkers that are currently being identified. In addition, trials will need to be adequately powered so as to be able to test for statistically significant clinical effectiveness differences within patient populations. New initiatives are in place to record detailed information on the precise chemotherapy (and targeted chemotherapy) regimens being used, together with data on age, cell type, stage of disease and performance status, allowing for very detailed observational audits of management and outcomes at a population level. It would be useful if these initiatives could be expanded to include the collection of health economics data.

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Contents

Glossary

Adenocarcinoma Cancer that begins in cells that line certain internal organs and that have glandular (secretory) properties.

Chemo-naive (**chemotherapy naive**) Having received no prior chemotherapy treatment.

Chemotherapy Treatment with anticancer drugs.

Chemoradiation Combined chemotherapy and radiation therapy.

Cost-effectiveness analysis Economic analysis that compares the costs and consequences (effects) of two or more courses of action. The consequences of the alternatives are measured in natural units, such as life-year(s) gained.

Heterogeneity Variability or differences between studies in the estimates of effects.

Histological diagnosis A diagnosis made by taking a sample of tissue or cells.

Intention to treat A method of data analysis in which all patients are analysed in the group they were assigned to at randomisation regardless of treatment adherence.

Locally advanced disease Stages IIIA/IIIB non-small cell lung cancer.

Large cell carcinoma A group of lung cancers in which the abnormal cells are large.

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

Metastasis The spread of cancer from one part of the body to another. Tumours formed from cells that have spread are called 'secondary tumours' and contain cells that are like those in the original (primary) tumour.

Metastatic disease Stage IV non-small cell lung cancer.

Mixed-treatment comparison An indirect comparisons of data that allows for the ranking of different treatments in order of efficacy and estimation of the relative treatment effect of competing interventions.

Non-small cell lung cancer A group of lung cancers that includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma.

Non-squamous cell carcinoma Includes adenocarcinoma and large cell carcinoma.

Quality-adjusted life-year(s) An index of survival that is weighted or adjusted by a patient's quality of life during the survival period. Quality-adjusted life-years are calculated by multiplying the number of life-years by an appropriate utility or preference score.

Relative risk The proportion of diseased people among those exposed to the risk factor divided by the proportion of diseased people among those not exposed to the risk factor.

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

Squamous cell carcinoma Cancer that begins in squamous cells, which are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts. Also called epidermoid carcinoma.

List of abbreviations

AC	Appraisal Committee
AE	adverse event
ASCO	American Society for Clinical Oncology
AUC	area under curve
BEV	bevacizumab
BNF	*British National Formulary*
BSC	best supportive care
BTOG2	British Thoracic Oncology Group Trial 2
CARB	carboplatin
CEA	cost-effectiveness analysis
CI	confidence interval
CIS	cisplatin
CMA	cost-minimisation analysis
CRD	Centre for Reviews and Dissemination
CT	computerised tomography
CUA	cost–utility analysis
DOC	docetaxel
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EGFR-TK	epidermal growth factor receptor-tyrosine kinase
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ERL	erlotinib
EU	European Union
FACT-L	Functional Assessment of Cancer Therapy – Lung questionnaire
FDA	US Food and Drug Administration
GEF	gefitinib
GEM	gemcitabine
GP	general practitioner
HR	hazard ratio
HRG	Healthcare Research Group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPASS	Iressa Pan ASian Study
ITT	intention to treat
i.v.	intravenous
KPS	Karnofsky Performance Status scale
LCSS	Lung Cancer Symptom Scale
LUCADA	National Lung Cancer Data Audit
LYG	life-year gained
LYS	life-year saved
MCMC	Markov Chain Monte-Carlo
MS	manufacturer's submission
MST	median survival time
M+	mutation positive (EGFR)
NEJGSG	North East Japan Gefitinib Study Group
NICE	National Institute for Health and Care Excellence

NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PAX	paclitaxel
PEM	pemetrexed
PFS	progression-free survival
PLAT	platinum (cisplatin or carboplatin)
PPS	postprogression survival
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RR	relative risk
SACT	Systemic Anti-Cancer Therapy
STA	single technology appraisal
TKI	tyrosine kinase inhibitor
TNM	tumour, node and metastasis
TOI	Trial Outcome Index
TTP	time to progression
UICC	Union for International Cancer Control
VNB	vinorelbine
WHO	World Health Organization
WJTOG	Western Japan Thoracic Oncology Group
WTP	willingness to pay

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

Scientific summary

Background

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK after breast cancer. In 2008, 40,806 new cases of lung cancer were diagnosed in the UK: 32,546 in England and 2403 in Wales. Lung cancer is rarely diagnosed in people aged < 40 years and 86% of cases occur in people aged > 60 years. In both men and women, smoking is the primary cause of lung cancer and prognosis is poor. Early-stage lung cancer is often asymptomatic, with two-thirds of patients diagnosed at a late stage.

In 2005 in the UK, the National Institute for Health and Care Excellence (NICE) produced comprehensive guidelines on the management of patients with lung cancer; these guidelines recommended chemotherapy for patients with non-small cell lung cancer (NSCLC): docetaxel (Taxotere®, Sanofi-aventis; DOC), gemcitabine (Gemzar®, Eli Lilly and Company; GEM), paclitaxel (Abraxane®, Celgene Corporation; PAX) or vinorelbine (Navelbine®, Pierre Fabre Pharmaceuticals Inc.; VNB) in combination with either cisplatin (CIS) or carboplatin (CARB) as standard first-line treatments for patients with locally advanced or metastatic disease. Further guidance has been published which recommends pemetrexed (Alimta®, Eli Lilly and Company; PEM) in combination with CIS as first-line treatment for patients with non-squamous locally advanced or metastatic disease and gefitinib (Iressa®, AstraZeneca; GEF) as a suitable first-line treatment for patients with epidermal growth factor receptor (EGFR) mutation-positive (M+) locally advanced or metastatic disease. The NICE guidelines for the diagnosis and treatment of lung cancer were partially updated in 2011. However, the current guidance on chemotherapy for patients with NSCLC has not been updated and there is therefore a need for the synthesis of current NICE guidelines with NICE guidance resulting from recent single technology appraisals. The objective of this report is to provide such a synthesis.

Objectives

The objective of the study was to evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic NSCLC. The results in this report relate solely to first-line systemic therapy for patients with locally advanced or metastatic NSCLC. No inference should be drawn from them regarding chemotherapy in any other context; this includes adjuvant therapy, combination therapy (with radiotherapy or surgery) or second-line and maintenance therapy. It is also important to recognise that, as in the delivery of all clinical care, there is a need to tailor treatments to the needs of individual patients and this will include the exploration of options and consideration of the risks and benefits of the various treatments available by the clinician in consultation with his or her patients.

Methods

Search strategy

Three electronic databases (MEDLINE, EMBASE and The Cochrane Library) were searched from January 1990 to August 2010 for randomised controlled trials (RCTs), systematic reviews and economic evaluations.

Patient populations

Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC were included.

Interventions and comparators
Studies that compared any first-line chemotherapy currently licensed in Europe and recommended by NICE were considered.

Outcomes
Data on any of the following outcomes were included in the assessment of clinical effectiveness: overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). For the assessment of cost-effectiveness, outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained.

Application of inclusion/exclusion criteria
Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any publication judged to be relevant by a reviewer was obtained and assessed for inclusion or exclusion. Two reviewers assessed the relevance of each publication; any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Data extraction and quality assessment
Data were extracted into a Microsoft Access 2007 database (Microsoft Corporation, Redmond, WA, USA). All trials were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance. The results of clinical and economic data extraction and quality assessment are summarised in the tables and narrative description.

Evidence synthesis
Where appropriate, relative treatment effects for OS, PFS, TTP and survival risk at years 1 and 2 were estimated using a standard meta-analysis for head-to-head comparisons between interventions based on intention-to-treat analyses. Mixed-treatment comparison methodology was used for the clinical effectiveness outcomes of OS, PFS, TTP and survival risk at 1 and 2 years.

Results

Of the 193 identified trials published since 2000, 23 trials compared chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination with a platinum (PLAT) drug for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Seven economic evaluations were identified from a possible 15 potential publications.

Quality assessment
Overall, the quality of the included RCTs was poorer than expected: there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials.

Clinical effectiveness review: efficacy data
All 23 clinical trials were published between 2001 and 2010 and included a total of 11,428 randomised patients. Of the 20 multicentre trials, six were international; the three single-centre trials were based in Taiwan. Seventeen trials were assessed as being sufficiently powered to evaluate OS. Median follow-up of patients ranged from 8 to 45 months. Doses of chemotherapy drugs varied, median number of chemotherapy cycles ranged from 2.6 to 6 and chemotherapy treaments were administered either by intravenous (i.v.) infusion or orally.

When the three GEF trials were compared with the other included trials, the proportion of males to females was much less; the percentage of males in the GEF trials ranged from 21% to 37%. These three

trials were conducted in East Asian countries and had somewhat different patient populations compared with the other trials. Two of these trials included only patients with EGFR M+ tumour status, and one trial included patients with pulmonary adenocarcinoma who were never-smokers or were former light smokers.

Twenty-three trials were included within the network of trials for the clinical analysis. The direct evidence for the NSCLC population with squamous disease included 18 trials (>7000 patients and >6000 deaths). These same 18 trials plus subgroup data from an additional two studies were included in the analysis of the NSCLC population with non-squamous disease. Participants of three studies, conducted entirely within East Asian countries, constituted the EGFR M+ NSCLC population. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and also very good consistency across individual trials in the within-group comparisons.

Among NSCLC patients with squamous disease, there were no statistically significant differences between any of the four chemotherapy regimens (DOC + PLAT, GEM + PLAT, PAX + PLAT, VNB + PLAT) in terms of increasing OS. However, both the direct and indirect evidence suggests a potential non-statistically significant advantage in terms of OS for GEM + PLAT [direct meta-analysis 1: hazard ratio (HR) = 1.08; 95% confidence interval (CI) 0.98 to 1.20] and for DOC + PLAT (direct meta-analysis 1: HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT. Analyses of 1- and 2-year survival support this conclusion.

For patients with non-squamous NSCLC there is borderline statistically significant evidence to suggest that PEM + PLAT increases OS compared with GEM + PLAT (direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00). However, there is no statistically significant evidence to suggest that PEM + PLAT compared with GEM + PLAT increases PFS (mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98).

Among patients with EGFR M+ status, OS was not statistically significantly different in those treated with GEF and those receiving PAX + PLAT or in those treated with GEF compared with those treated with DOC + PLAT. There was a statistically significant improvement in PFS among those patients treated with GEF compared with those treated with DOC + PLAT or PAX + PLAT. However, there was significant quantitative heterogeneity between the two trials comparing GEF with PAX + PLAT, which requires further exploration.

It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. The relative clinical effectiveness of PEM + PLAT in patients who are EGFR M+ is unknown.

Clinical effectiveness review: adverse events

Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower severe AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported.

Clinical effectiveness review: quality of life

Twelve trials reported QoL outcomes using a variety of instruments/tools. Seven trials reported no significant difference in QoL and four trials reported some significant differences between treatment groups. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting.

Cost-effectiveness review: summary

None of the seven included studies were directly relevant to decision-making in the NHS because they are not UK focused and/or they do not estimate incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY gained.

Summary of Assessment Group's cost-effectiveness results

A total of 12 first-line chemotherapy regimens were incorporated into the economic model developed by the Assessment Group (AG): five primary licensed products [DOC, GEM, PAX, VNB (i.v. and oral)] used in combination with either CIS or CARB, PEM in combination with CIS, and GEF monotherapy. First-line chemotherapy regimens with the same primary agent but different PLAT therapy differ only in terms of treatment costs. A lifetime perspective is taken in the model and costs and benefits are discounted at 3.5% per annum. In the base-case analysis, *British National Formulary* (BNF) prices are used and in the sensitivity analysis, electronic market information tool (eMIT) prices are used; probabilistic sensitivity analysis results are also provided.

Economic results: patients with squamous disease

The four third-generation chemotherapy agents, when used in combination with PLAT for first-line treatment of advanced or metastatic NSCLC, are often considered to exhibit similar effectiveness, when compared in terms of standard statistical measures (e.g. *p*-values). However, the mixed-treatment comparison analysis undertaken by the AG which informs the current model does indicate important differences which, when combined with differences in the management of the condition and acquisition cost, provide a basis for differentiating between treatment options and arriving at some robust conclusions:

- In both deterministic and probabilistic analyses for both the base-case and alternative pricing scenarios, VNB doublets yield the least patient benefit (as measured by expected discounted QALYs), and are not the least expensive option. As a result, VNB cannot be considered to provide either optimal effective or cost-effective chemotherapy treatment.
- PAX doublets are consistently minimum cost options and therefore represent the initial 'good value' treatment, to be supplanted only if an alternative option yields greater benefit at an acceptable 'willingness-to-pay' (WTP) threshold.
- The choice of preferred alternative main agent to PAX generally favours DOC over GEM as its greater effectiveness appears to outweigh the additional acquisition cost, although both lie on the efficiency frontier.

Economic results: patients with non-squamous disease

The addition of a PEM doublet to the four third-generation chemotherapy agents changes the relationship between the regimens, because of the clear outcome advantage of PEM therapy in terms of the improved expected survival of patients with non-squamous disease. However, the high price of branded PEM compared with the other drugs (in most cases available generically) means that PEM is preferred on cost-effectiveness grounds only if the WTP threshold is set > £37,000 per QALY (or £50,000 per QALY if eMIT prices are assumed). This means that PAX remains a viable treatment (and possibly GEM and DOC). However, VNB is clearly not cost-effective in either scenario.

Economic results: patients who are epidermal growth factor receptor mutation positive

The base-case analyses for GEF compared with the two chemotherapy doublets (PAX and DOC) for which evidence is available show poor cost-effectiveness for GEF. Results are improved somewhat by disaggregating the three GEF trials, but even then cost-effective ICERs (< £30,000 per QALY gained) are obtained only for the second alternative scenario [Western Japan Thoracic Oncology Group (WJTOG) trial only] based on the smallest RCT comparing GEF with the DOC + CIS doublet.

Discussion

Using BNF prices the AG has demonstrated that CIS doublets are preferred to CARB doublets. For patients with squamous disease, moving from low to moderate WTP thresholds, preferred drugs are: PAX → GEM → DOC. For patients with non-squamous disease, a similar pattern of ranking applies: PAX → GEM → DOC. However, PEM + CIS has improved OS compared with all other recommended treatments in patients with non-squamous disease, but PEM + CIS is relatively expensive and a high threshold is required before PEM + CIS can be considered cost-effective (up to £35,000 per QALY gained). For patients with EGFR M+, comparing GEF to PAX and DOC yields very high ICERs. For all populations, using eMIT prices means that CARB doublets are generally preferred to CIS doublets and drug administration costs become more important than drug acquisition costs. The AG is aware that the economic results rely on the limited clinical data available. Modelling of costs and benefits reveals that there are often only slight differences between treatments in terms of clinical effectiveness yet when these differences are modelled over the longer term (> 12 months) and the costs of the treatments are taken into consideration, then differences in cost-effectiveness begin to appear.

The treatment of patients with NSCLC is complex. In contrast to previous research, recent clinical effectiveness evidence from RCTs demonstrates that patient health outcomes depend not only on the treatment received but also on the characteristics of the patient population participating in the trial and of the cancer subtypes. Patients with NSCLC are not a homogeneous group; increasingly trials are distinguishing between three populations of patients (patients with squamous disease, patients with non-squamous disease and patients who are EGFR M+). The clinical effectiveness and cost-effectiveness evidence for each of the three patient populations needs to be reviewed separately.

As the prices of generic chemotherapy fall and new treatments become available, it is also prudent to consider cost-effectiveness using both BNF and eMIT prices. From the results of the economic evaluations described in this report it is clear that the size of the decision-makers' WTP threshold influences the range of treatments considered to be cost-effective.

Limitations

The limitations of the report can be summarised as follows: very few trials reported QoL data; AEs from the different trials were difficult to compare; CARB and CIS were treated as being similarly effective in the clinical analyses; and owing to the large volumes of data available for patients with lung cancer, the methods employed in the review do not always match the methods stated in the original protocol. Finally, the quality of the included trials was poorer than anticipated and this finding must be taken into consideration when interpreting the results of the clinical and economic analyses presented.

Conclusion

This comprehensive *Health Technology Assessment* review is unique to the field of NSCLC research in that it compares all of the regimens currently licensed in Europe and approved by NICE for the first-line systemic treatment of patients with advanced NSCLC. This review may assist clinicians to make decisions regarding the treatment of patients with advanced NSCLC as new evidence related to the important subgroups of patients becomes available in published form.

Research recommendations

The design of future lung cancer trials needs to reflect the influence of factors such as histology, genetics and the new prognostic biomarkers that are currently being identified. In addition, trials will need to be adequately powered so as to be able to test for statistically significant clinical effectiveness differences within patient populations. New initiatives are in place to record detailed information on the precise chemotherapy (and targeted chemotherapy) regimens being used, together with data on age, cell type,

stage of disease and PS, allowing for very detailed observational audits of management and outcomes at a population level. It would be useful if these initiatives could be expanded to include the collection of health economics data.

Implications for practice

Closer examination of clinical effectiveness and cost-effectiveness data means that we have been able to provide a comprehensive framework of information for three subpopulations of patients with NSCLC that clinicians can refer to as they attempt to balance patient factors, available treatments, treatment costs and AEs in their daily decision-making.

Concluding remarks

The completion of this review has taken a significant length of time and during that period there has been explicit acknowledgement in the published literature of the important differences in the characteristics of patients who previously were identified as having NSCLC. It is anticipated that no further RCTs will be carried out involving patients with NSCLC as a homogeneous group, but that consideration of the important patient subgroups will take precedence and allow for the development of more specialised and targeted treatments which, in turn, will require RCTs of increasingly sophisticated design.

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Chapter 1 Background

Description of health problem

Incidence and prevalence

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK after breast cancer. In 2008, 40,806 new cases were diagnosed in the UK: 32,546 in England and 2403 in Wales.[1] Lung cancer is rarely diagnosed in people aged < 40 years and 86% of cases occur in people aged > 60 years.[1] *Table 1* provides an overview of lung cancer statistics in the UK. The European age-standardised incidence rate of lung cancer in 2008 was 45.6 per 100,000 population in England and 52.2 per 100,000 population in Wales.[1] The UK incidence rate in males is similar to incidence rates in most of Western Europe and lower than those in most of Eastern Europe. The UK incidence rate in females is one of the highest rates in the European Union (EU).[1] There is an increased incidence of lung cancer in individuals from the lowest socioeconomic strata.[2–4] In 2008, around 65,000 individuals were living with lung cancer in the UK,[1] the majority of them male.[1]

Causation

Smoking causes around 90% of lung cancer deaths in men and > 80% of lung cancer deaths in women in the UK.[5] Other causes include radon exposure, air pollution, heredity and occupational exposures such as asbestos and industrial chemicals.[6]

Survival

There were 35,261 lung cancer-related deaths in the UK in 2008.[1] Prognosis is very poor; lung cancer is usually asymptomatic in the early stages and two-thirds of patients are diagnosed at a late stage when curative treatment is not possible. Twenty-seven per cent of male and 30% of female lung cancer patients in England and Wales survive for 1 year; 7% and 9%, respectively, survive 5 years.[1] According to the National Lung Cancer Data Audit (LUCADA) 2006–8, the median survival for individuals with lung cancer in England is 203 days (interquartile range 62–545 days).[7]

There are many factors that affect lung cancer survival rates, including smoking status, general health, sex, race and cancer treatments. For example, survival rates at 1 and 3 years are significantly higher among Asian than white lung cancer patients, regardless of age.[1]

TABLE 1 Lung cancer statistics in the UK (data extracted from Cancer Research UK)[1]

Lung cancer – UK	Males	Females	Total
Number of new cases (UK 2008)	22,846	17,960	40,806
Rate per 100,000 population[a]	59.4	37.6	47.8
Number of deaths (UK 2008)	19,868	15,393	35,261
Rate per 100,000 population[a]	51.0	32.0	40.3
One-year survival rate (for patients diagnosed 2004–6, England)	27%	30%	–
Five-year survival rate (for patients diagnosed 2004–6, England)	7%	9%	–

a Age-standardised to the European population.

Diagnosis

Lung cancer at an early stage is usually asymptomatic and, thus, diagnosis is often at a late stage. Unfortunately, two-thirds of patients are diagnosed when the cancer has already metastasised. Across England and Wales a significant proportion of each age group presents with late-stage metastatic disease.[8] According to recently updated National Institute for Health and Care Excellence (NICE) guidelines,[7] urgent referral for a chest radiograph should be offered when a patient presents with haemoptysis or any of the following unexplained or persistent (i.e. lasting >3 weeks) symptoms or signs:

- cough
- chest/shoulder pain
- dyspnoea
- weight loss
- chest signs
- hoarseness
- finger clubbing
- features suggestive of metastasis from a lung cancer (e.g. in brain, bone, liver or skin)
- cervical/supraclavicular lymphadenopathy.

There are various techniques for diagnosing and staging non-small cell lung cancer (NSCLC) in the UK. The updated guidelines[7] for the diagnosis and treatment of lung cancer recommend that if a chest radiograph or computerised tomography (CT) scan suggests lung cancer, patients should be offered an urgent referral usually to a chest physician, who should choose further investigations that give the most information about diagnosis and staging with the least risk to the patient.

Within this diagnostic process there are a number of key issues that need to be addressed including histology, epidermal growth factor receptor (EGFR) mutation status, disease staging, performance status (PS) and the presence of comorbid disease.

Disease staging

The stage of lung cancer at diagnosis reflects the degree of spread of cancer and is crucially important to determine which patients have potentially curative disease, and which do not, and this helps to define a patient's prognosis. TNM (tumour, node and metastasis) classification provides a system for staging the extent of cancer. *Table 2* shows the seventh edition of the Union for International Cancer Control (UICC) TNM system[9] for classification of NSCLC disease stage. T refers to the size of the primary tumour, N refers to the involvement of the lymph nodes and M refers to the presence of metastases or distant spread of the disease. It should be noted that all of the trial evidence in this review would have used the UICC sixth edition (or lower), as the seventh edition has only been implemented in the UK since January 2010. *Table 2* compares the stage from the sixth edition, which has been modified, with the new stage in the seventh edition. *Table 3* shows the surgical stage groupings in the seventh TNM classification.

Performance status

Performance status is used to quantify cancer patients' general well-being and may be used to determine whether or not a patient is fit enough to receive chemotherapy, whether or not a chemotherapy dose adjustment is necessary, and to quantify how much supportive care a patient may require. There are three main scales used to measure PS: the World Health Organization (WHO) PS scale,[10] the Karnofsky Performance Status (KPS) scale[10] and the Eastern Cooperative Oncology Group (ECOG) PS scale.[11] A summary of the WHO PS scale is shown in *Table 4* as this is the most commonly used scale in clinical practice in the UK.[10] A score of 0 on the WHO scale indicates a patient is completely able to look after him/herself and a score of 4 indicates that a patient requires a lot of support.

TABLE 2 The TNM staging of the NSCLC seventh edition compared with the sixth edition

Sixth edition	Seventh edition	
TNM stage	TNM stage	Descriptor
T1	T1a	Maximum dimension ≤ 2 cm
	T1b	Maximum dimension 2–3 cm
T2	T2a	Maximum dimension 3–5 cm
	T2b	Maximum dimension 5 –7 cm
	T3	Maximum dimension > 7 cm
T4	T3	Additional nodule in same lobe
M1	T4	Additional nodule in ipsilateral different lobe
M1	M1a	Additional nodules in contralateral lung
M1	M1a	Ipsilateral pleural effusion

TABLE 3 Surgical stage groupings in the seventh TNM classification

Stage	T	N	M
0	Tis	N0	M0
IA	T1a, b	N0	M0
IB	T2a	N0	M0
IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1, 2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
IIIB	T4	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1a, b

TABLE 4 The WHO PS criteria

Scale	WHO criteria[10]
0	Patient is fully active and more or less the same as before illness
1	Patient is unable to carry out heavy physical work, but can do anything else
2	Patient is up and about more than half the day, able to look after him/herself, but not well enough to work
3	Patient is in bed or sitting in a chair for more than half the day, needs some help in looking after him/herself
4	Patient is in bed or a chair all the time and needs a lot of looking after

Histology

Non-small cell lung cancer accounts for approximately 84% of all lung cancers diagnosed and the remaining 16% are small cell lung cancers. The main subtypes of NSCLC are squamous cell carcinoma (33%) and non-squamous cell carcinoma (29%); the latter is made up of adenocarcinoma (25%) and large cell carcinoma (4%). Approximately 36% of patients are listed as having NSCLC 'not-otherwise specified' and 1% as having carcinoma in situ.[12]

Squamous cell carcinoma commonly begins in the bronchi, centrally in the lungs. Adenocarcinoma starts in the periphery of the lungs and can tend to be present for a long time before it is detected. It is the type of lung cancer usually found in non-smokers and is the most common type seen in women. Large cell carcinomas often occur in the outer regions of the lungs, and tend to grow rapidly and spread more quickly than some other forms of NSCLC.[13]

Histological confirmation (i.e. a diagnosis made by taking a sample of tissue or cells) is an important element of diagnosis because it helps to determine a patient's treatment pathway. However, it is noted that histological confirmation is not always straightforward and there are several key issues that must be noted. For example, tumour heterogeneity in the context of small histological or cytological samples size, interobserver variation, the absence of centralised pathology review, and the lack of any tested biological hypothesis which explains this observation that some drugs do better when the term squamous is applied to the biopsy and some when it is not.

Despite these cautions, more and more treatments are being recommended for different types of patients as recent evidence suggests that newer drugs are beneficial in certain histological subtypes of NSCLC. For example, pemetrexed (Alimta®, Eli Lilly and Company; PEM) is beneficial in patients with non-squamous carcinoma.[13] (Note: PEM is licensed and recommended for use in patients with adenocarcinoma and large cell carcinoma; however, for the purposes of this report we refer to the use of PEM in patients with non-squamous disease.) A significant proportion of patients are diagnosed based on clinical examination and radiological investigations alone, without histological evidence. According to LUCADA, in England and Wales, histological confirmation of the cancer diagnosis is made in 72% of cases, although there is wide (regional) variation from 25% to >85%.[14] Given that more chemotherapy options are becoming available which alter the potential treatment pathway of a patient, histological testing is expected to be carried out more frequently and in a more standardised way in the future. Recent NICE guidance for the first-line treatment of NSCLC recommends histological testing and, therefore, histological testing rates are expected to increase.[7] The proportion of patients diagnosed as having disease 'not otherwise specified' will decrease in time [and the proportion of patients with non-squamous and EGFR mutation-positive (M+) disease will gradually rise], although regional variation will inevitably continue.

Epidermal growth factor receptor mutation status

Improvements in the understanding of the molecular and biological basis of lung cancer have led to the identification of a number of drugs that target proteins on cancer cells for the treatment of lung cancer. Among the most studied is EGFR tyrosine kinase inhibitors (TKIs), which target proteins on cancer cells and are an effective treatment for patients with tumours with activating mutations of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK)[15] (EGFR M+) and are often referred to as part of a group of treatments labelled 'targeted chemotherapy'. Analysis of predictive tumour markers is necessary to identify patients with EGFR M+ who would then be candidates for such targeted treatment.[16]

Clinical consensus is that EGFR M+ status will be present in around 10% of patients within the overall population. A study by Rossell *et al.*[17] found that 17% of Spanish patients with non-squamous NSCLC were EGFR M+. There are various clinical and lifestyle factors associated with the likelihood of the presence of EGFR mutation; for example, the rate of EGFR M+ status is higher among East Asian female non-smokers with adenocarcinoma than among white British male smokers with squamous cell carcinoma. EGFR mutation status can act as both a predictor of response to chemotherapy treatment (identification of subgroups of populations that would benefit from EGFR-targeted therapy) and a prognostic factor (indicator or the likely natural course of the disease).

Current service provision

Two linked but independent processes guide provision of care for patients with NSCLC in the UK. The European Medicines Agency (EMA) is a centralised agency of the EU that is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. In the UK, EMA approval, through the granting of marketing authorisation, does not automatically guarantee patient access to those medicines. At the request of the Department of Health, NICE provides guidance to the NHS in England and Wales on the clinical effectiveness and cost-effectiveness of selected new and established technologies for NSCLC by undertaking appraisals of these technologies. The NHS is legally obliged to fund and resource medicines and treatments that are recommended based on the results of NICE technology appraisals.

The National Institute for Health and Care Excellence produces clinical guidance and guidelines recommending appropriate treatments and care for people with NSCLC, the recommendations are based on the best available clinical effectiveness and cost-effectiveness evidence. Comprehensive guidelines[18] on the management of patients with NSCLC published by NICE in 2005 recommended docetaxel (Taxotere®, Sanofi-aventis; DOC), gemcitabine (Gemzar®, Eli Lilly and Company; GEM), paclitaxel (Abraxane®, Celgene Corporation; PAX) and vinorelbine (Navelbine®, Pierre Fabre Pharmaceuticals Inc.; VNB) for the first-line treatment of patients with locally advanced or metastatic NSCLC.

However, since the release of the guidelines a number of NICE single technology appraisals (STAs) have evaluated other treatment regimens. STAs evaluate a single technology for a single indication. These have included PEM for patients with adenocarcinoma and large cell carcinoma,[13] GEF as a first-line treatment for EGFR M+ patients,[16] PEM for patients with adenocarcinoma and large cell carcinoma in the maintenance setting,[19] erlotinib (Tarceva®, Roche Products Limited and Roche Diagnostics Limited; ERL) in the second-line setting[20] and ERL in the maintenance setting.[21] Planned STAs include cetuximab (Erbitux®, Merck Serono) in the first-line setting[22] and ERL for the first-line treatment of patients with EGFR-TK M+ NSCLC.

There has been no systematic or comprehensive examination of the clinical effectiveness and cost-effectiveness of the current chemotherapy recommendations. New and updated guidelines[7] include recommendations on communication, diagnosis and staging, selection of patients for treatment with curative intent, surgical techniques, smoking cessation, combination treatment for NSCLC, treatment of small cell lung cancer, managing endobronchial obstruction, managing brain metastases, and follow-up and patient perspectives. Given that the guidelines[7] reflect the status of treatment preferences reflected in a number of recent NICE appraisals and the complexity of the clinical issues and changes in drug prices (as generics become available and Patient Access Schemes are applied), it can be confusing for health professionals to determine the most cost-effective chemotherapy for an individual patient.

Treatment options for non-small cell lung cancer

It would be useful to define chemotherapy options before discussing treatment options in detail. Chemotherapy is the treatment of cancer using chemical substances. Chemotherapy drugs work to destroy cancer cells by preventing them from multiplying. Treatment consists of either a chemotherapeutic agent or a molecularly targeted agent such as EGFR. Chemotherapies are generally non-specific in cellular action; they preferentially target rapidly proliferating cells and do not discriminate between malignant and non-malignant cells.

Figure 1 shows a treatment pathway for patients with NSCLC and shows estimates of the proportions and numbers of patients with NSCLC along the treatment pathway in England and Wales based on histology and staging data, NICE guidelines[7] and NICE guidance.[26,27] Recommendations for patients with small cell lung cancer are not discussed in this report.

Thirty per cent of patients with NSCLC are diagnosed with stage I–IIIA disease (personal communication with Dr Michael Peake, Glenfield Hospital, using unpublished LUCADA data from 2009). These patients are

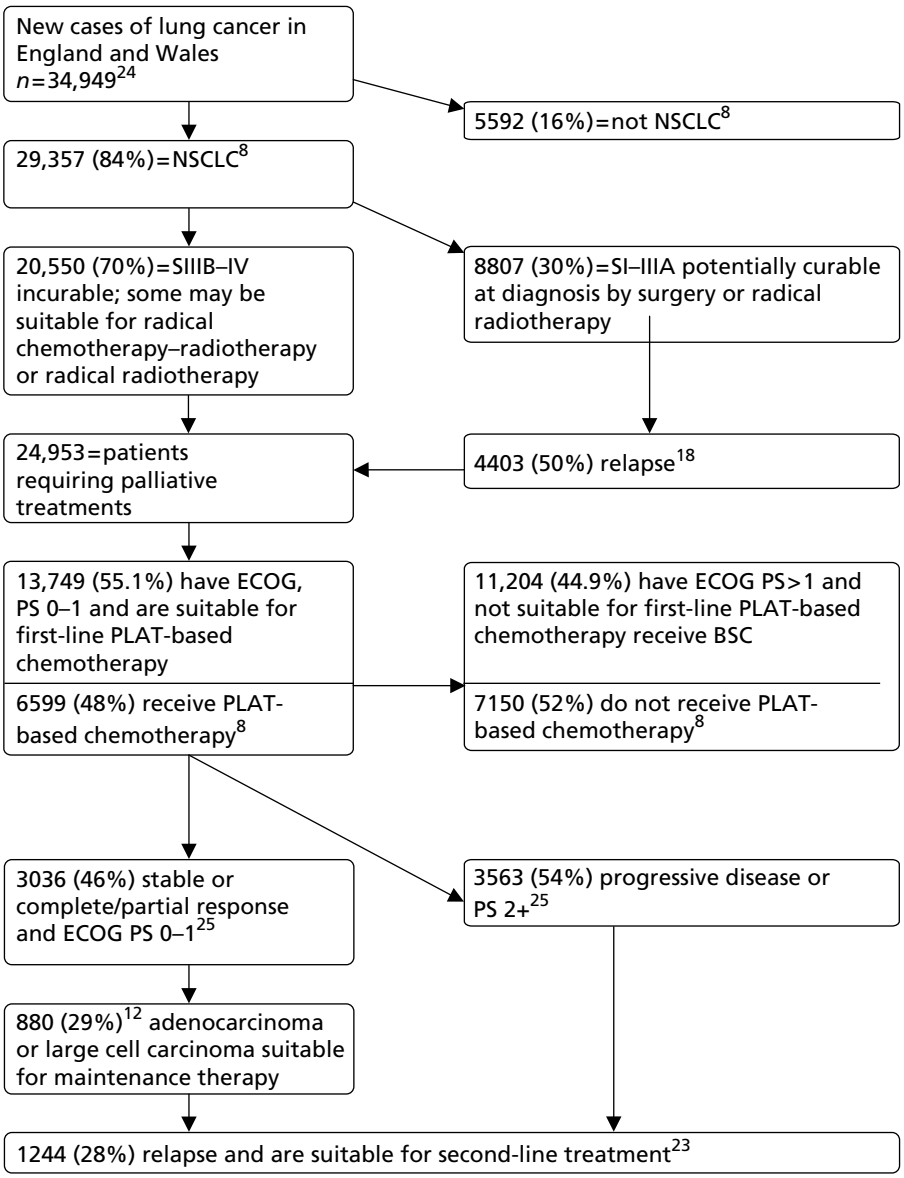

FIGURE 1 Treatment pathway for patients with NSCLC. BSC, best supportive care; PLAT, platinum.

suitable for potentially curative surgery or radical radiotherapy. Surgery for NSCLC consists of lobectomy, pneumonectomy and wedge resection. Approximately 50% of patients undergoing these procedures will relapse and will then be eligible for further treatment.[18] Patients with stage IIIA–IIIB disease who are not amenable to surgery can be treated with potentially curative chemoradiation.

Seventy per cent of patients with NSCLC have stage IIIB or IV disease and a PS of 0 or 1 at the time of diagnosis. These patients are assessed for their suitability for first-line chemotherapy; less than half (48%) of patients who are assessed actually receive it.[8] Among those who receive chemotherapy, almost half will respond to treatment and have either a complete or a partial response. Of these patients, a relatively small proportion can go on to have maintenance treatment and only 28% are suitable for second-line chemotherapy.[23]

The majority of patients with NSCLC are diagnosed late and have metastatic or locally advanced disease. Therefore, up to 50% of patients are treated with best supportive care (BSC) alone. During all stages of treatment, patients receive BSC or 'active supportive care' in addition to any anticancer treatment. In the recently published lung cancer guidelines,[7] NICE defines 'supportive care' as 'the multidisciplinary holistic

care offered to all patients and their carers throughout the pathway to help them cope with cancer and treatment of it. Best supportive care packages include options for information giving, symptom control and psychological, social and spiritual support. Palliative care provides a similar holistic approach, but is specific to those patients with advanced progressive illness' (p. 98).[7]

First-line treatment options for patients with NSCLC are shown in *Figure 2*. Less than 70% of patients with NSCLC have stage IIIB or stage IV disease, which equates to 20,433 patients. The percentage of patients in each stage is from 2009 audit data (M Peake, personal communication). The proportion of patients receiving BSC, chemotherapy, radiotherapy and surgery, stratified by stage is derived from LUCADA data for 2009 (personal communication with Dr Paul Beckett, Queens Hospital, using unpublished LUCADA data from 2009). These proportions have been applied to the most up-to-date incidence rates for NSCLC in England and Wales.[24] It should be noted that disease stage was recorded in 81% of cases and that these cases represent 98% of expected incidence cases for 2009; therefore, as a result of these missing data the total percentage of patients receiving BSC, radiotherapy, chemotherapy and surgery ranges from 70% to 94% within each disease stage (and does not equal 100%). In addition, the percentage of people receiving radiotherapy includes both those receiving radical and those receiving palliative treatment.

Outcome measures

Survival is considered the most reliable cancer end point within a randomised controlled trial (RCT), and when trials can be conducted to adequately assess survival it is usually the preferred end point. Overall survival (OS) is measured as the time from randomisation to death from any cause; median survival is the point in time at which 50% of people with a condition will have died and 50% are still alive. Year-1 and -2 survival risks are defined as the probability of survival in intervals of time elapsed from randomisation to years 1 and 2, respectively.

The majority of trials also report progression-free survival (PFS) as an intermediate surrogate measure of survival. PFS measures the length of time between randomisation until tumour progression or death from any cause; unlike OS, PFS is not an unequivocal outcome measure and is often determined by how frequently patients are monitored.

Tumour progression is defined as at least a 20% growth in the size of the tumour or spread of the tumour since the beginning of treatment.[28] Time to progression (TTP) is defined as the time from randomisation until tumour progression (and does not include death). The majority of RCTs also measure overall response rate (ORR), which is the proportion of people who show a response (the tumour shrinks), which can be complete or partial. Stable disease is recorded when there is no response and the tumour does not change in size. Stable disease also means that no new tumours have developed and that the cancer has not spread to any new regions of the body.[28]

Adverse event (AE) and quality-of-life (QoL) data are also measures of important clinical benefit and provide information on how well chemotherapy is tolerated. In patients with advanced NSCLC, palliative chemotherapy is given to improve QoL. The EuroQol 5D (European Quality of Life-5 Dimensions; EQ-5D) is a standardised generic instrument for measuring health-related quality of life (HRQoL). It provides a utility score for health and a self-rating of HRQoL. Other commonly used QoL tools within NSCLC trials are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30[29] and the lung cancer-specific module QLQ-LC13,[30] the Lung Cancer Symptom Scale (LCSS)[31] and the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire.[32] Both AEs resulting from the disease itself and those due to chemotherapy have a considerable impact on HRQoL.[33]

Despite QoL being both a vitally important measure of a patient's general emotional, physical and mental well-being and a very relevant measure of the 'success' of chemotherapy treatment primarily because advanced stage NSCLC is not curable, a minority of trials address QoL issues. When QoL has been examined, patients receiving chemotherapy report better scores compared with patients receiving BSC alone.[34]

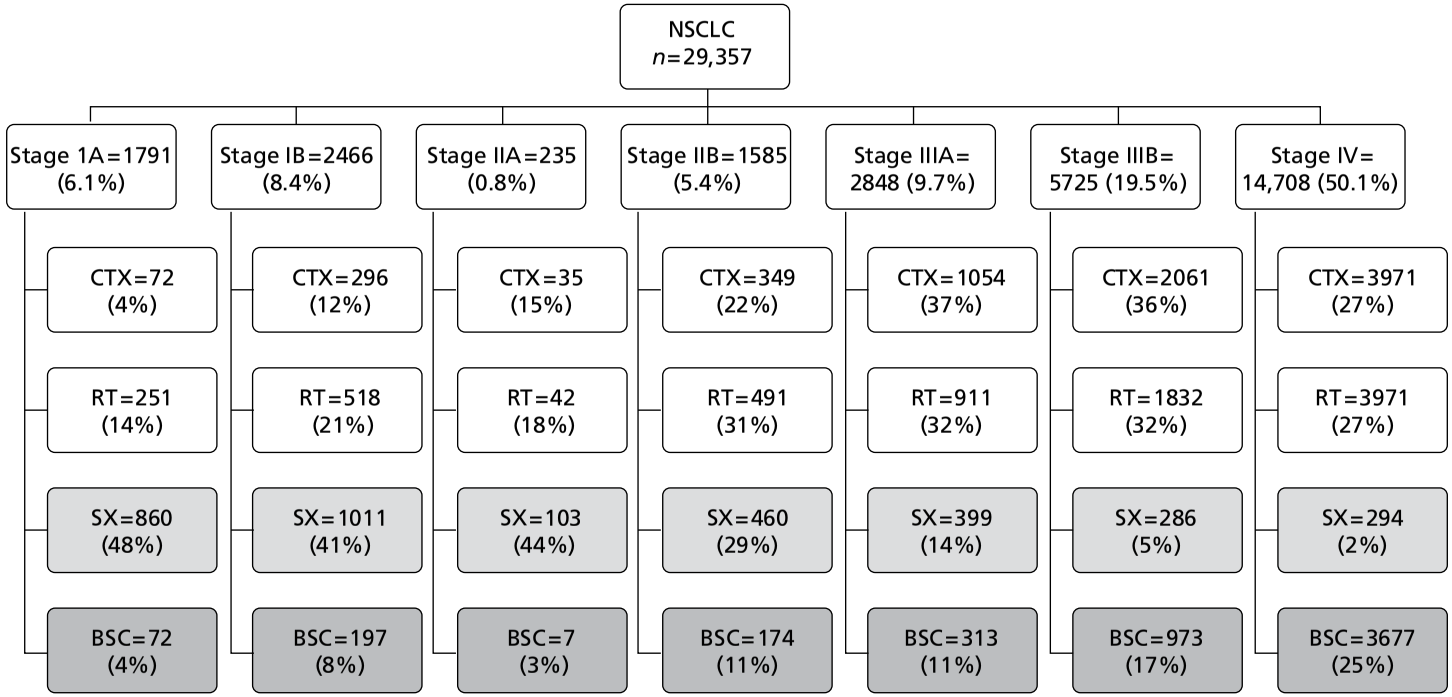

FIGURE 2 Treatment options for patients with NSCLC in the first-line setting. CTX, chemotherapy; RT, radiotherapy; SX, surgery.

Current UK guidelines and guidance

In terms of first-line treatment, NICE guidelines[7] recommend that chemoradiation is the first choice of treatment for patients with stage IIIA disease and is also an option for patients with stage IIIB disease who have good PS (WHO 0–1 or KPS 80–100) and localised disease that can be safely encompassed in a radical radiotherapy treatment volume. These patients are a very different and much smaller group of patients than patients receiving palliative chemotherapy. Chemotherapy is the first choice of treatment for patients with stage IIIB and stage IV NSCLC assessed as being of WHO PS 0–1.[7] BSC (including palliative radiotherapy) is the first choice of treatment for patients with stage IV WHO PS 3–4, following medical optimisation.

The NICE guidelines[7] recommend that first-line chemotherapy for advanced NSCLC should be a combination of a third-generation drug (DOC, GEM, PAX or VNB) and a platinum (PLAT) – either carboplatin (CARB) or cisplatin (CIS). According to the updated NICE guidelines,[7] whether CARB or CIS is used depends on the balance of toxicity, efficacy and convenience. Patients who are unable to tolerate a PLAT combination may be offered single-agent chemotherapy with a third-generation drug.[7]

Following STAs of PEM and gefitinib (Iressa®, AstraZeneca; GEF), NICE also recommends that PEM plus CIS be considered as a first-line therapy for patients with locally advanced or metastatic NSCLC who are histologically confirmed as having large cell or adenocarcinoma.[13] GEF as a single agent is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC who test positive for the EGFR-TK mutation.[16] *Table 5* summarises the licensed indications and recommendations set out by NICE which govern the use of chemotherapy as a first-line treatment for patients with locally advanced or metastatic NSCLC in England and Wales.

The patient chemotherapy treatment pathway

Following the publication of guidelines by NICE in 2005,[18] PLAT-based doublet chemotherapy has become established as the standard first-line treatment for patients with advanced NSCLC and good PS in the UK. Data from a large observational pan-European trial[35] show that four cycles of PLAT-based chemotherapy treatment is standard practice in England and Wales. *Figure 3* presents a flow diagram of the patient treatment pathway for first-line treatment of NSCLC and an estimate of the proportions of patients along the pathway. The proportion of patients who have non-squamous disease and are treated with PEM or GEM is unknown.

Availability of therapeutic agents

Table 6 lists the costs of available branded and generic preparations as taken from the *British National Formulary* (BNF).[38] AstraZeneca provides a Patient Access Scheme decreasing the cost of GEF to the NHS. In addition, clinical centres frequently negotiate prices below those listed in the BNF.[38] Over the past few years, the patents for a number of these agents have expired and they are now available in generic formulations which are less expensive. The currently available data on costs are discussed more fully in *Chapter 4*.

Reasons for conducting this review

The most recent comprehensive review of chemotherapy treatments for patients with NSCLC was conducted in 2001 by Clegg *et al.*[39] and was integral to the development of the NICE guidelines for the diagnosis and treatment of lung cancer in 2005.[18] The Clegg *et al*. review[39] focused on three first-line drugs and their use in all patients with NSCLC: PAX, GEM and VNB. At the time of the Clegg *et al*. review,[39] DOC was not licensed for the first-line treatment of patients with lung cancer in Europe. However, in 2005 when NICE's lung cancer guidelines were first published,[18] DOC had received a licence for use in this patient population and was therefore included in the guidelines alongside PAX, GEM and VNB and recommended as a standard first-line treatment.

TABLE 5 Current NICE recommended first-line chemotherapy for NSCLC

Treatment	NICE recommendations	Licensed indication (Summary of Product Characteristics)	Common AEs
Docetaxel (DOC) (Taxotere®, Sanofi-aventis; Docetaxel Teva Pharma®, Actavis UK Ltd) Taxane Blocks the growth of cancer cells by preventing cell division i.v. Steroids given to prevent allergic reaction	DOC + PLAT[22] (Single agent if intolerant) First line Stages III and IV Good PS (WHO 0–1/KPS 80–100)	Taxotere in combination with CIS is indicated for the treatment of patients with unresectable, locally advanced or metastatic NSCLC, in patients who have not previously received chemotherapy for this condition Docetaxel Teva Pharma in combination with CIS is indicated for the treatment of patients with unresectable, locally advanced or metastatic NSCLC, in patients who have not previously received chemotherapy for this condition	Allergic reaction presenting as flushing, skin reactions, itching, chest tightness, back pain, difficulty breathing, fever or chills, swelling, weight gain, stomach upsets, alopecia, cardiac irregularities and tiredness
Gefitinib (GEF) (Iressa®, AstraZeneca) Protein kinase inhibitor Blocks the protein EGFR which is involved in the growth and spread of cancer cells Oral	NICE TA 192[27] First line Patients with EGFR-TK M+ status Stages III and IV Manufacturer must provide at fixed price agreed under Patient Access Scheme	Iressa is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK	Diarrhoea, vomiting, nausea, skin reactions such as an acne-like rash, which is sometimes itchy with dry and/or cracked skin, loss of appetite, weakness, dry, red or sore mouth and increased level of alanine aminotransferase
Gemcitabine (GEM) (Gemzar®, Eli Lilly and Company) Cytotoxic agent Kills dividing cells including cancer cells i.v.	GEM + PLAT[22] (Single agent if intolerant) First line Stages III and IV Good PS (WHO 0–1/KPS 80–100)	Gemzar in combination with CIS is indicated as a first-line treatment of patients with locally advanced (inoperable stage IIIA or IIIB) or metastatic (stage IV) NSCLC Gemzar is indicated for the palliative treatment of adult patients with locally advanced or metastatic NSCLC	Myelosuppression, lethargy, flu-like symptoms, rashes, nausea and vomiting and hair loss

Treatment	NICE recommendations	Licensed indication (Summary of Product Characteristics)	Common AEs
Paclitaxel (PAX) (Abraxane®, Celgene Corporation) Taxane Blocks the growth of cancer cells by preventing cell division i.v. Steroids given to prevent allergic reaction	PAX + PLAT[22] (Single agent if intolerant) First line Stages III and IV Good PS (WHO 0–1/KPS 80–100)	PAX in combination with CIS is indicated for the treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiotherapy	Allergic reactions: blood disorders, fever, unusual bleeding or unexplained bruising, heart problems, high or low blood pressure, numbness, joint or muscle pain, liver disorders, nausea, diarrhoea, sore mouth and tongue, hair loss, skin reactions and swelling at injection site
Pemetrexed (PEM) (Alimta®, Eli Lilly and Company) Antifolate Blocks three separate enzyme targets vital to the survival of cancer cells i.v. Given with folic acid tablets and vitamin B_{12} injections	NICE TA 181[26] PEM + CIS Patients with non-squamous histology: adenocarcinoma and large cell First line Stages III and IV	Alimta in combination with CIS is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology	Fatigue, nausea, loss of appetite, rash, diarrhoea and sore mouth
Vinorelbine (VNB) (Navelbine®, Pierre Fabre Pharmaceuticals Inc.) Vinca alkaloid Stops cell division of affected cells and causes cell death i.v./oral	VNB + PLAT[22] (Single agent if intolerant) First line Stages III and IV Good PS (WHO 0–1/KPS 80–100)	Navelbine as a single agent or in combination is indicated for the first-line treatment of stage III or IV NSCLC	Myelosuppression, nausea and vomiting, constipation, weakness, peripheral neuropathy, alopecia and injection site pain

i.v., intravenous; TA, technology appraisal.

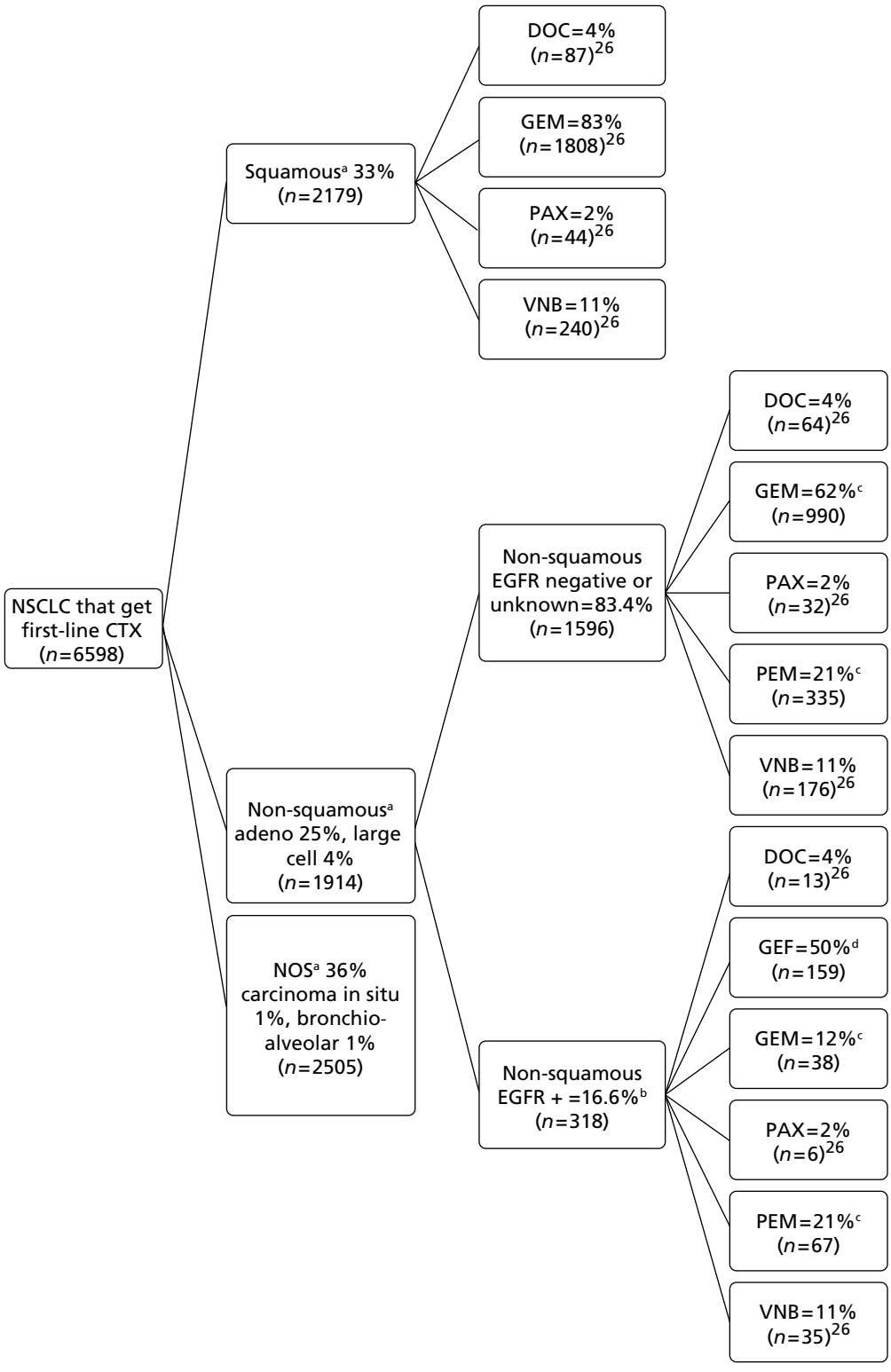

FIGURE 3 Patient first-line chemotherapy treatment pathway in England and Wales. a, The Information Centre for Health and Social Care, 2007;[12] b, Rossell *et al.,* 2009;[17] c, best estimate; d, Epsicom Business Intelligence Ltd.[36,37] CTX, chemotherapy.

TABLE 6 Chemotherapy agents, costs and manufacturers

Chemotherapy agent	Manufacturer	Strength	Presentation	Cost	Comments
DOC	Sanofi-aventis	20 mg/ml	Vials: 20 mg/1 ml, 80 mg/4 ml, 160 mg/8 ml	20 mg = £162.75, 80 mg = £543.75, 160 mg = £1069.50	Taxotere First licensed DOC product
	Actavis	10 mg/ml	Vials: 20 mg/0.5 ml, 40 mg/1 ml, 80 mg/2 ml		Requires reconstitution, solvent included
	Actavis	20 mg/ml	Vials: 20 mg/1 ml, 80 mg/4 ml, 140 mg/7 ml		
	Hospira	10 mg/ml	Vials: 20 mg/2 ml, 80 mg/8 ml, 160 mg/16 ml		
	medac	20 mg/ml	Vials: 20 mg/1 ml, 80 mg/4 ml, 140 mg/7 ml		Taxceus
GEF	AstraZeneca	250 mg	Tablets	30 = £2167.71	Iressa
GEM	Eli Lilly and Company	38 mg/ml after reconstitution	Vials: 200 mg, 1 g	200 mg = £32.55, 1 g = £162.76	Gemzar First licensed GEM product
	Actavis		Vials: 200 mg, 1 g, 2 g	200 mg = £32, 1 g = £162, 1.5 g = £213.93, 2 g = £324.00	
	Hospira		Vials: 200 mg, 1 g, 2 g		
	medac		Vials: 200 mg, 1 g, 1.5 mg		
	Sun		Vials: 200 mg, 1 g		
PAX	Bristol-Myers Squibb	6 mg/ml			Taxol First licensed PAX product, discontinued in 2008
	Celgene Corporation	5 mg/ml	Vials: 100 mg		Not licensed for lung cancer
	Actavis	6 mg/ml	Vials: 30 mg/5 ml, 100 mg/16.7 ml, 150 mg/25 ml, 300 mg/50 ml	30 mg = £66.85, 100 mg = £200.35, 150 mg = £300.52, 300 mg = £601.03	
	Hospira				
	medac		Vials: 30 mg/5 ml, 100 mg/16.7 ml, 300 mg/50 ml		
PEM	Eli Lilly and Company	25 mg/ml	Vials: 100 mg, 500 mg	100 mg = £160.00, 500 mg = £800.00	Alimta
VNB	Pierre Fabre Pharmaceuticals Inc.	10 mg/ml	Vials: 10 mg/1 ml, 40 mg/4 ml, 50 mg/5 ml	10 mg = £29.75, 50 mg = £139.98	Navelbine First licensed VNB product
		20 mg, 30 mg, 80 mg	Capsules	20 mg = £43.98, 30 mg = £65.98, 80 mg = £175.92	
	Actavis	10 mg/ml	Vials: 10 mg/1 ml, 50 mg/5 ml	10 mg = £29.00, 50 mg = £139.00	
	medac				

Since 2005, the NICE appraisal process has evolved and additional recommendations from the STA process have made the clinical pathway more complicated. In addition, generic preparations for a number of the chemotherapy agents have become available resulting in a need to re-examine the cost-effectiveness of some of the drugs. Finally, research in this area appears to be at a crossroads because recent research related to histology and genetics has demonstrated important differences within the NSCLC population and the focus of clinical trials is changing. The Clegg *et al*. review[39] served as a basis for decisions related to the clinical effectiveness of chemotherapy treatments compared with BSC. For ethical reasons, new chemotherapy drugs used in the first-line setting will not be compared with BSC, they will need to be compared with currently available therapies. In addition, there has been recent identification of specific subgroups of patients who may respond to treatment in different ways and it is expected that future research will identify more, and the clinical pathway will become even more complex.

The goal of the review is to provide a succinct overview of the now complex clinical evidence relating to clinical effectiveness and AEs and match this to the cost-effectiveness evidence for the first-line treatment of patients with NSCLC. This review aims to inform current and future guidelines, assist policy makers in deciding how the newer chemotherapy agents (e.g. PEM and GEF) fit into the current treatment pathway for patients in the NHS in England and Wales, and provide clinicians with a framework for decision-making related to the treatment options available for patients with NSCLC.

Chapter 2 Definition of the decision problem

Decision problem

The population of interest is adult patients who are chemotherapy-naive, with locally advanced or metastatic NSCLC, who are not suitable for treatment with curative intent.

Analysis was restricted to chemotherapy drugs currently licensed in Europe and approved by NICE for the first-line treatment of patients with locally advanced and metastatic NSCLC:

- PLAT-based chemotherapy (CARB or CIS) in combination with DOC, GEM, PAX, VNB
- PEM + CIS
- single-agent therapy – GEF.

The primary outcome was OS. Secondary outcomes were:

- PFS
- time to disease progression
- survival risk
- ORRs
- AEs
- HRQoL
- incremental cost per life-year gained (LYG)
- incremental cost per quality-adjusted life-year (QALY) gained.

Overall aims and objectives of assessment

The objectives of the assessment are to evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic NSCLC. Second-line, third-line and maintenance treatments are not included in the assessment.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

In order to ensure that adequate clinical input into the review was obtained an Advisory Panel, comprised of clinicians and experts in the field, was established. The role of this panel was to answer specific clinical questions and comment on the draft report.

Identification of trials

The systematic review was guided by the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[40] A comprehensive search strategy was developed; search terms included a combination of index terms (e.g. non-small-cell lung carcinoma) and free-text words (e.g. lung cancer or lung tumour or lung carcinoma). The search of MEDLINE and EMBASE was restricted to papers with abstracts published in the English language. MEDLINE was searched from January 1990 to March week 3 2009 and EMBASE was searched from January 1990 to week 13 2009. The Cochrane Library (including Cochrane Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials and Health Technology Assessments) was searched up to Issue 3, July 2010. An updated search was performed of MEDLINE and EMBASE to identify trials published up until August 2010. All references were exported to the EndNote version X4 (Thomson Reuters, CA, USA). Searches have been limited to these databases based on the evidence related to searching presented by Royle and Waugh,[41] which demonstrates that wider searching is not always effective in retrieving additional trials for inclusion in a specific group of diseases including cancer. Details of the search strategies are available in *Appendix 1*.

The protocol was revised to exclude trials that had been published prior to the year 2000, owing to the large number of references identified by the searches and to reflect recent advances in chemotherapy treatments (e.g. third-generation chemotherapy drugs). The protocol is available in *Appendix 2*.

A number of hand searches were carried out to ensure the completeness of the review including the database of the American Society for Clinical Oncology (ASCO) and the US Food and Drug Administration (FDA) and EMA websites. A key review of chemotherapy treatments for patients with NSCLC by Clegg *et al.*[39] was searched for relevant trials. Reference lists of included trials were also searched to identify any further relevant trials.

Inclusion and exclusion

The inclusion/exclusion assessment by each reviewer was recorded on a pretested, standardised form. The citations identified by the search strategy were assessed for inclusion; reviewers independently screened all the titles and abstracts identified by electronic searching of MEDLINE, EMBASE and The Cochrane Library (Issue 3, July 2010). The search of MEDLINE and EMBASE was updated to August 2010. Potentially relevant references were obtained as full-text copies and each reference was assessed independently by two reviewers using the inclusion and exclusion criteria outlined in *Table 7*.

Data extraction strategy

Data extraction forms were developed and piloted on a sample of included trials. Data were extracted on trial design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer. Microsoft Access software (Microsoft Corporation, Redmond, WA, USA) was used to store extracted data from the included trials. *Appendix 3* contains details of data extraction.

TABLE 7 Inclusion criteria (clinical effectiveness) based on the decision problem

Patient population	Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC
Intervention	Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE including: • PLAT-based chemotherapy (CARB or CIS) in combination with DOC, GEM, PAX or VNB • PEM + CIS • Single-agent therapy – GEF
Comparators	Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE for the first-line treatment of patients with locally advanced and metastatic NSCLC
Study Design	RCTs Systematic reviews
Outcomes	OS PFS Time to disease progression 1- and 2-year survival rates ORRs AEs HRQoL

Critical appraisal strategy

All included trials were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination (CRD) guidance[42] for undertaking reviews in health care and adapted to reflect the characteristics of patients with NSCLC. Data relating to quality assessment were extracted by one reviewer and independently checked for accuracy by a second reviewer. *Appendix 4* contains the quality assessment criteria. Where necessary, disagreements between reviewers were discussed in consultation with a third reviewer to achieve consensus.

Evidence synthesis

Analysis was restricted to chemotherapy drugs currently licensed in Europe and approved by NICE. Recent clinical evidence from PEM-based trials has suggested significant interaction between PEM efficacy and tumour histology and indicates that histology is critical in choosing the appropriate therapy for patients with NSCLC. Based on these data, NICE recommends that PEM in combination with CIS may also be considered as a first-line therapy for patients with locally advanced or metastatic NSCLC with disease histologically confirmed as large cell or adenocarcinoma.[13] Similarly, evidence from GEF-based trials indicates that GEF efficacy depends on the presence of sensitising EGFR mutations in the tumour. GEF is recommended by NICE as an option for the first-line treatment of locally advanced or metastatic NSCLC that tests positive for the EGFR-TK mutation.[16] Recent trial evidence, therefore, supports the concept that treatment choices in the first-line management of advanced NSCLC should no longer be the same for all patients with NSCLC, but rather decisions must take into consideration tumour histology subtyping and also molecular profiling.

To reflect current UK treatment pathways, analyses were undertaken and reported for three subpopulations of NSCLC: patients with predominantly squamous disease, patients with predominantly non-squamous disease and patients who were EGFR M+. In the main, all analyses were conducted on the total population according to randomisation; however, subpopulation data were included in our analyses if used previously for international or national decision-making.

Patients with squamous disease can be treated with any of the third-generation drugs (DOC, GEM, PAX or VNB) in combination with PLAT. Very few published RCTs differentiate between subpopulations of patients. We assume that the results of all studies that do not differentiate between subpopulations are equally

applicable to patients with squamous disease and non-squamous disease. Before adopting this approach, we identified four third-generation studies[43–46] that reported multivariate statistical testing and included histology as a candidate explanatory variable. From our critique of these studies, we concluded that there was no significant influence of histology on outcomes for patients with squamous or non-squamous disease. In this review, all data applicable to the squamous population were derived from mixed population studies; however, none of the studies included in the review investigated the use of chemotherapy solely for patients with squamous disease.

Patients with non-squamous disease who are not EGFR M+ can be treated with either third-generation drugs in combination with PLAT or PEM + CIS. This means that the data available to support treatment decisions for patients with non-squamous disease may be derived from analyses of total (mixed) population studies as well as from RCTs where survival analyses by histology may have been undertaken. Use of subpopulation data means that survival analyses were not conducted on the total trial population according to randomisation. Subpopulation data regarding the use of PEM have been used as the basis for the award of European marketing authorisation and regulatory decision-making, we therefore considered use of these subpopulation data in our analyses to be reasonable and appropriate.

Patients who are EGFR M+ can be treated with either third-generation drugs in combination with PLAT or GEF. Again, subpopulation data regarding the use of GEF have been used as the basis for the award of European marketing authorisation and regulatory decision-making, we therefore considered use of subpopulation data in our analyses to be reasonable and appropriate.

Data on any of the following outcomes were included in the meta-analyses: OS; survival at 1 and 2 years, PFS and TTP. Definitions of PFS and TTP varied between trials and the PFS and TTP outcomes in all of the included trials were assessed for eligibility for inclusion in analyses. No evidence synthesis was attempted for QoL, AEs and ORR owing to limited data or variability in outcome assessment.

Both direct head-to-head meta-analysis and mixed-treatment comparison approaches were undertaken in order to integrate information on the relative efficacy of all included drugs as an insufficient number of trials were available that directly compared all treatment options. When sufficient data permitted, analyses were undertaken for the squamous population, the non-squamous population and the EGFR M+ population.

For the analyses of the population with squamous disease, trials for PEM and GEF were excluded. Therefore, the following analyses on OS, PFS and TTP were planned. The primary analyses in the population with squamous disease were direct meta-analysis 1 and mixed-treatment comparison 1. The remaining analyses were all sensitivity analyses to explore the impact of particular trials or characteristics on results from the primary analyses: the sensitivity analyses were undertaken to explore the impact of six cycles of chemotherapy, different combinations of chemotherapy and PLAT, and trials with < 24 months follow-up.

Primary analyses: population with squamous disease:

- Direct meta-analysis 1: standard direct head-to-head meta-analysis using data from four licensed third-generation agents (PAX, VNB, DOC and GEM) from 18 trials.[47–60] This included four pair-wise meta-analyses for the following comparisons: GEM + PLAT compared with VNB + PLAT, GEM + PLAT compared with PAX + PLAT, VNB + PLAT compared with PAX + PLAT and VNB + PLAT compared with DOC + PLAT. Data for two comparisons (GEM + PLAT vs DOC + PLAT, PAX + PLAT vs DOC + PLAT) were available from single trials and, therefore, no direct meta-analysis was undertaken.
- Mixed-treatment comparison 1: mixed-treatment comparison using data from four licensed third-generation agents (PAX, VNB, DOC and GEM) from 18 trials.[47–60] The analysis included direct and indirect evidence from all six pair-wise comparisons: GEM + PLAT compared with VNB + PLAT, GEM + PLAT compared with PAX + PLAT, VNB + PLAT compared with PAX + PLAT, VNB + PLAT

compared with DOC + PLAT, GEM + PLAT compared with DOC + PLAT and PAX + PLAT compared with DOC + PLAT.

Sensitivity analyses: population with squamous disease:

- Direct meta-analysis A and mixed-treatment comparison A: sensitivity analysis excluding Chen *et al*.[52] (< 24 months follow-up time) and Tan *et al*.[59] (used six cycles of chemotherapy).
- Direct meta-analysis B and mixed-treatment comparison B: sensitivity analysis using data from PAX + CIS instead of PAX + CARB from the Schiller *et al*.[47] trial.
- Direct meta-analysis C and mixed-treatment comparison C: sensitivity analysis using data from DOC + CARB instead of DOC + CIS from the Fossella *et al*.[44] trial.
- Direct meta-analysis D and mixed-treatment comparison D: sensitivity analysis excluding Tan *et al*.[59] (used six cycles of chemotherapy).
- Direct meta-analysis E and mixed-treatment comparison E: sensitivity analysis excluding Chen *et al*.[52] (< 24 months follow-up time). This affects VNB + PLAT compared with DOC + PLAT pair-wise comparison.

For the population with non-squamous disease, the following analyses on OS and PFS were planned.

Primary analyses: population with non-squamous disease:

- Direct meta-analysis 1: standard direct head-to-head meta-analysis using data from four licensed third-generation agents (PAX, VNB, DOC and GEM) from 18 trials[47–60] and two PEM studies.[61,62] This included five pair-wise meta-analyses for the following comparisons: GEM + PLAT compared with VNB + PLAT, GEM + PLAT compared with PAX + PLAT, VNB + PLAT compared with PAX + PLAT, VNB + PLAT compared with DOC + PLAT and GEM + PLAT compared with PEM + PLAT. Data for two comparisons (GEM + PLAT vs DOC + PLAT and PAX + PLAT vs DOC + PLAT) were available from single trials and, therefore, no direct meta-analysis was undertaken.
- Mixed-treatment comparison 1: mixed-treatment comparison using data from four licensed third-generation agents (PAX, VNB, DOC and GEM) from 18 trials[47–60] and two PEM studies.[61,62] The analysis included direct and indirect evidence from all 10 pair-wise comparisons: GEM + PLAT compared with VNB + PLAT, GEM + PLAT compared with PAX + PLAT, GEM + PLAT compared with DOC + PLAT, GEM + PLAT compared with PEM + PLAT, VNB + PLAT compared with PAX + PLAT, VNB + PLAT compared with DOC + PLAT, VNB + PLAT compared with PEM + PLAT, PAX + PLAT compared with DOC + PLAT, PAX + PLAT compared with PEM + PLAT and DOC + PLAT compared with PEM + PLAT.

The following sensitivity analyses were undertaken to explore the impact of six cycles of chemotherapy, different combinations of chemotherapy and PLAT, trials with < 24 months follow-up and the one study[62] with PEM + CARB which is not licensed in the UK.

Sensitivity analyses: population with non-squamous disease:

- Direct meta-analysis A and mixed-treatment comparison A: sensitivity analysis excluding Chen *et al*.[52] (< 24 months follow-up time) and Tan *et al*.[59] (used six cycles of chemotherapy).
- Direct meta-analysis B and mixed-treatment comparison B: sensitivity analysis using data from PAX + CIS instead of PAX + CARB from the Schiller *et al*.[47] trial.
- Direct meta-analysis C and mixed-treatment comparison C: sensitivity analysis using data from DOC + CARB instead of DOC + CIS from the Fossella *et al.*[44] trial.
- Direct meta-analysis D and mixed-treatment comparison D: sensitivity analysis excluding Tan *et al*.[59] (used six cycles of chemotherapy).
- Direct meta-analysis E and mixed-treatment comparison E: sensitivity analysis excluding Chen *et al*.[52] (< 24 months follow-up time).

- Direct meta-analysis F and mixed-treatment comparison F: sensitivity analysis excluding Gronberg *et al*.[62] (contains PEM + CARB which is not licensed in the UK).

For the EGFR M+ population, the following analyses on OS and PFS were planned:

- Direct meta-analysis 1: standard direct head-to-head meta-analysis including two trials.[15,63,64]
- Mixed-treatment comparison A: analysis including three GEF trials.[15,63–65]
- This analysis includes both direct and indirect evidence for all three trials.

Adverse events

This review focuses on AEs that were categorised in the published trials as being grades 3 and 4. It was anticipated that the AEs would be reported in a disparate fashion that would not be amenable to meta-analysis and, if this was the case, then AEs would be summarised in tabular format. Significant differences in AEs between chemotherapy treatment groups within trials are highlighted, as well as the top 10 AEs that occurred within chemotherapy treatment regimens. These top 10 AEs have been summarised by extracting all AE data from each trial, grouping similar AEs and calculating the weighted average of the proportion of each AE according to each chemotherapy treatment.

Direct evidence synthesis

All analyses for the NSCLC population with squamous disease were based on the intention-to-treat (ITT) population where possible and as noted above, included a mix of patients with squamous and non-squamous disease. For non-squamous and EGFR M+ populations, data from trials[15,62,63] were based on the results of subgroup analyses. Where appropriate, standard meta-analysis were undertaken for each pair-wise treatment comparison using the 'metan' command within Stata Version 9.2 (StataCorp LP, College Station, TX, USA). For time-to-event outcomes (OS, PFS and TTP), the trial level estimate of log-hazard ratio (HR) and its variance were extracted directly from trial publications if available. Additional data were requested whenever needed from the authors of trials that directly compared first-line chemotherapy treatments currently licensed in Europe and approved by NICE. These additional data were requested in order to include as many relevant trials as possible in the meta-analysis. Details of additional data requested and provided are presented in *Appendix 5*. In the absence of direct estimates from published papers or requested from the authors, previously reported methods that use published data such as Kaplan–Meier survival curves or log-rank statistics were used to estimate the required trial-level log-HR and its variance.[66,67] A random-effects (frequentist) inverse variance-weighted approach was used to pool estimates of log-HR across trials.

In economic modelling, both short- and long-term survival data are always preferred when projecting survival benefits for a technology over a lifetime period using the best available evidence. This evidence is normally derived from a meta-analysis as the most appropriate summary statistic because this takes into account both the number of events and the time to these events, and also the data from those patients who have been censored. However, trial reports do not always report time to event data. Therefore, in order to address this, 1-year and 2-year survival data were extracted from trial reports, along with the number randomised to each treatment group to estimate the risk ratio within each trial and used a random effects Mantel–Haenszel approach to calculate the pooled risk ratio with a 95% confidence interval (CI). Although 1-year and 2-year survival analysis was specifically designed to inform economic modelling, this summary measure has some limitations, especially when follow-up and censoring patterns vary from trial to trial. One approach would be to adjust for variable follow-up and censoring across trials. However, in this analysis, not all trials reported the censoring rates and for simplicity, we assumed that these factors were comparable across trials.

Statistical heterogeneity was assessed by considering the chi-squared test for heterogeneity with a 10% level of significance, and the I^2-statistic with a value of 50% representing moderate heterogeneity.[68,69]

Mixed-treatment comparison – direct and indirect comparisons

As trials conducting head-to-head comparisons of all treatments under evaluation were not available or insufficient for some comparisons, the possibility of conducting an indirect comparison was investigated. This approach fulfils the objective of providing simultaneous comparison of all the relevant treatment alternatives, and can provide information about the associated decision uncertainty or sufficient information for economic evaluation. Hence, for the purposes of decision-making, a Bayesian mixed-treatment comparison framework was adopted to synthesise information on all technologies simultaneously using Markov Chain Monte Carlo (MCMC) methods to estimate the posterior distributions for our outcomes of interest. The MCMC simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. The mixed-treatment comparison analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different treatments in order of efficacy and estimation of the relative treatment effect of competing interventions. This approach assumes exchangeability of treatment effect across all included trials, such that the observed treatment effect for any comparison could have been expected to arise if it had been measured in all other included trials. This was assessed informally through examination of the trial populations and comparability of outcomes in the common treatment group facilitating the comparison. Inconsistency in the treatment effects between pair-wise comparisons were investigated by comparing the direct and indirect evidence together with the 95% CIs.

As with all meta-analyses, mixed-treatment comparison may be conducted using either fixed- or random-effects models. Random-effects models allow for the possibility that the true treatment effect may differ between trials. In our analyses, random-effects models were used throughout. Model fit was assessed based on residual deviance and deviance information criteria. Adjustment for multiarm trials was performed since estimates of relative treatment effects from trials with more than two treatment arms will be correlated owing to their joint dependence with the reference treatment arm.

In each MCMC simulation, we ranked the absolute log-hazard then used it to calculate the probability that each treatment was best across all simulations.[70,71] If a treatment is significantly better than all other treatments in the mixed-treatment comparison, the probability of it being the most effective treatment will be at least 95%. A probability <95% indicates that there is at least one other treatment which is not significantly different to the best treatment (at the 5% level). A non-informative (flat prior) normal distribution was used for the log-HR and log-relative risk (RR) of each relative comparison; thus, the observed results are completely influenced by the data and not the choice of prior.

WinBUGS version 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK) was used for the mixed-treatment comparison analysis by adapting code (presented in *Appendix 6*) from the Multi-Parameter Evidence Synthesis Research Group.[72] Two chains were used to ensure that model convergence was met after 90,000 iterations with a burn-in of 10,000. Formal convergence of the models was assessed using trace plots and the Gelman–Rubin approach[73] and through inspection of the history plots. OS, PFS and TTP results were expressed as HRs with 95% CI.

Results of review of clinical effectiveness

Quantity of research available

As shown in *Figure 4*, the electronic searches identified 5378 citations (*Table 8* describes in detail the results of the database searching). Initial screening identified 330 potentially relevant references; these were obtained as full-text copies, and the 240 references that were published post 2000 were assessed for eligibility for inclusion. Of the 223 trials, 30 trials were excluded because they were not chemotherapy versus chemotherapy comparisons. Information regarding the 17 RCTs that were excluded from the 240 references found from electronic searching are listed, with reasons for exclusion, in *Appendix 7*.

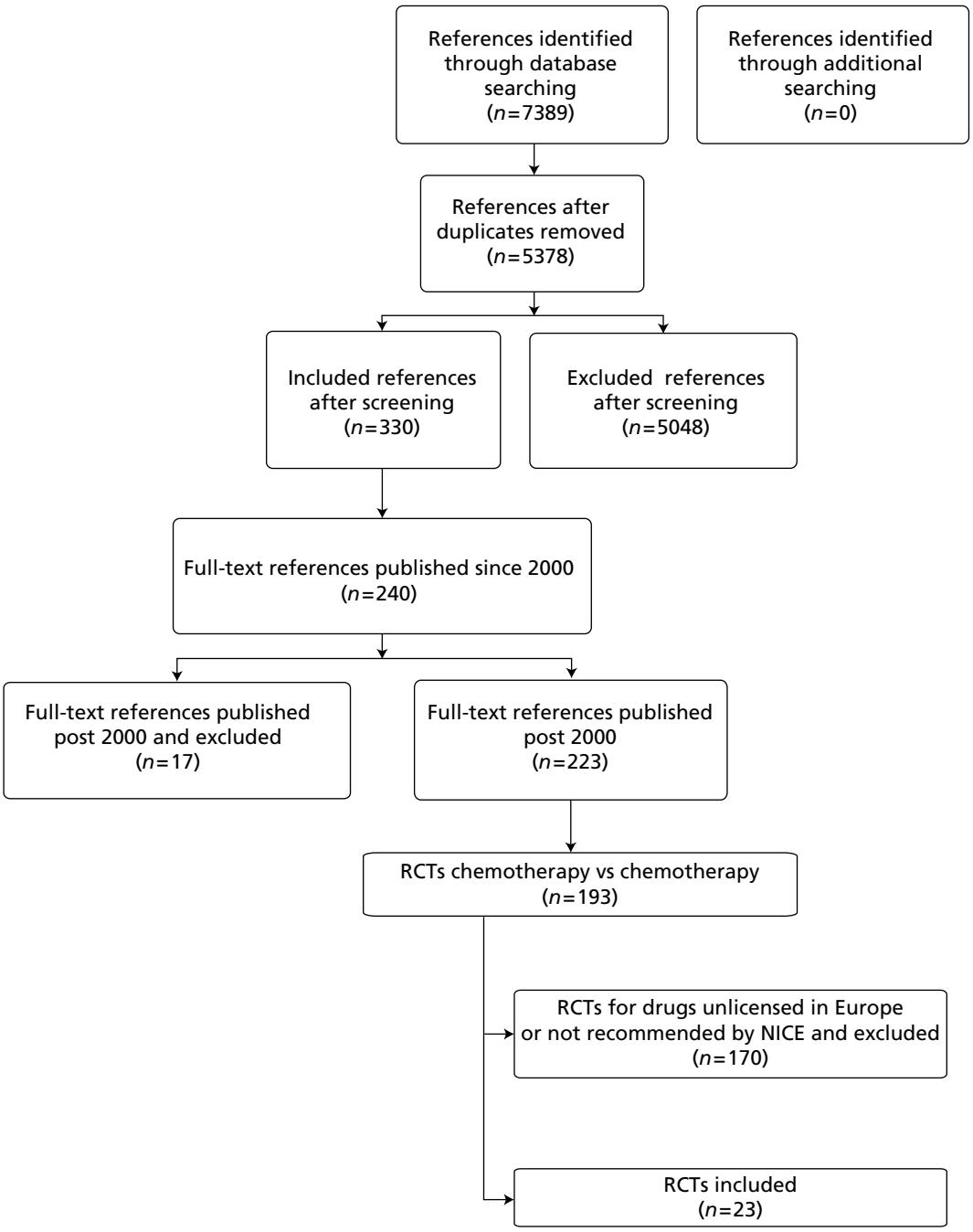

FIGURE 4 Flow diagram of inclusion of trials.

The database of abstracts from the ASCO annual NSCLC meetings up to and including 2010 was searched to identify any relevant trials from details of conference abstracts. Three abstracts were identified as potentially relevant for inclusion; however, full-text articles could not be found of any of the three abstracts.[74–76]

Overall, 193 trials compared chemotherapy with chemotherapy, of which 23 trials (reported in 24 publications[15,47–65]) compared chemotherapy drugs currently licensed in Europe and recommended by NICE for the first-line treatment of patients with locally advanced or metastatic NSCLC.

TABLE 8 Results of database searches

Database	Dates	Number	Deduplicated	First screen	Second screen	Chemotherapy unlicensed in Europe or not recommended by NICE	Excluded	Chemotherapy vs chemotherapy
MEDLINE	1990 to March week 3 2009	2594	3848	329	265	136 references, 126 trials and 10 linked references	10	18 references, 17 trials and one linked reference
EMBASE	1990 to week 13 2009	3034						
MEDLINE	2009 to August week 3 2010	316	455	35	34	23	0	6
EMBASE	2009 to week 34 2010	370						
CCTR	2000 to Issue 3 of 4 July 2010	1034	1034	174	31	21	7	0
CDSR	2000 to Issue 3 of 4 July 2010	4	4	0	0	0	0	0
DARE	2000 to Issue 3 of 4 July 2010	22	22	0	0	0	0	0
HTA	2000 to Issue 3 of 4 July 2010	15	15	0	0	0	0	0
Total no. of references		7389	5378	538	330	180	17	24
Total no. of RCTs (see *Figure 4*)						**170**	**17**	**23**

CCTR, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment.

Assessment of clinical effectiveness

Quality

Full details of the quality assessment criteria are presented in *Appendix 4*. Results of the methodological quality assessment of trials are presented in *Table 9*. Overall, methodological quality of included trials was poor. Only six[15,43,45,55,57,64,65] of the 23 included trials reported sufficient information for them to be assessed as adequately randomised and with adequate concealment of random allocation.

All trials clearly reported the number of participants randomised. All trials reported eligibility criteria and, with the exception of four trials,[48,56,58,60] all trials reported details about co-interventions, for example palliative radiotherapy and/or second-line chemotherapy (in one trial[54] a minority of patients had surgery following chemotherapy). In the trial by Douillard *et al.,*[53] second-line therapy was built into the trial design; however, nearly all trials (appropriately) allowed second-line treatments which could potentially confound results. Five trials[15,44,58,62,64,65] were reported as open, i.e. assessors, administrators and participants were not blinded; two studies[59,63] blinded the assessors. In 16 studies[43,45–57,60,61] the authors did not state whether or not blinding of participants, investigators or outcome assessors was carried out. The outcomes of >80% of patients were assessed in all studies and all studies reported reasons for dropout; 10 trials[15,44,48,49,51–53,59–61,64] used an ITT approach to assess OS. Five of the trials[48,53,57,60,61] appeared to report fewer outcomes than initially stated.

Bias can occur as a result of the early closure of trials;[77] it is noted that three of the included trials were stopped early.[47,49,65] In the trial by Gebbia *et al.,*[49] further accrual into the two 'sequential chemotherapy' arms [in this case meaning GEM + ifosfamide (Mitoxana®, Baxter Healthcare Ltd) followed by VNB + CIS or the opposite sequence, which are two group comparisons not included within this review] was stopped because the VNB + CIS arm appeared to be more effective. Owing to initial slow accrual, the protocol of the trial by Mitsudomi *et al.*[65] was amended to include patients with stage IIIB/IV disease and to allow outsourcing of EGFR genetic testing in order to further facilitate patient accrual. Accrual was halted when investigators considered the trial to be sufficiently powered, making further accrual of patients unnecessary, and final analyses were done on the available data. In the trial by Schiller *et al.*,[47] after the first 68 patients, accrual of the PS 2 cohort was halted owing to a high incidence of AEs, including five deaths (subsequent analysis showed that only two of the five deaths were clearly treatment related). All trials provided reasons for withdrawal; see *Table 23* for actual numbers of patients treated.

Trial characteristics

Trial characteristics are presented in *Appendix 8*. The 23 trials were published between 2001 and 2010. Of the 20 multicentre trials, six have international centres.[15,44–46,59,61,64] The three single-centre trials were all located in Taiwan.[50–52] All included trials were published in English.

There are five Phase II trials,[51–53,56,58] 16 Phase III trials[15,43–46,48,49,54,55,57,59–65] and two trials[47,50] with phase undefined. Ten trials[15,43,44,53,57–62,64] were funded solely by pharmaceutical companies, five trials[46,47,56,63,65] were funded by research grants, two trials[45,48] were funded by both pharmaceutical companies and research grants and funding was not stated in six trials.[49–52,54,55]

Seventeen trials[15,43–48,51–54,57,60–62,64,65] were sufficiently powered to evaluate OS, four trials[49,56,59,63] were inadequately powered and the power of two trials[50,58] was unclear. (If a trial reported an estimated sample size and then randomised at least this number of patients, then the trial was assessed as sufficiently powered.) Median follow-up ranged from 11 to 40 months.

Details of trial interventions are presented in *Appendix 9*. Four trials[43,44,46,60] compared three treatment arms and three trials[47,49,57] compared four treatment arms (not all arms met the inclusion criteria for this analysis). *Table 10* shows the chemotherapy comparisons which were available from the 23 included trials. Trials using either CARB or CIS are both described as including PLAT.

TABLE 9 Quality assessment

Trial	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified
	Truly random	Allocation concealment	Number stated	Presented	Achieved[a]		
Kelly 2001[48]	NS	NS	✓	✓/✗	NS	✓	NS
Scagliotti 2002[43]	✓	✓	✓	✓	NS	✓	✓
Schiller 2002[47]	NS	NS	✓	✓/✗	NS	✓	✓/✗
Fossella 2003[44]	NS	✓	✓	✓	✓	✓	✓
Gebbia 2003[49]	NS	✓	✓	✓	NS	✓	✓
Gridelli 2003[45]	✓	✓	✓	✓	NS	✓	✓
Smit 2003[46]	✓	NS	✓	✓	NS	✓	✓
Chen 2004[51]	NS	NS	✓	✓	✓	✓	✓
Douillard 2005[53]	NS	NS	✓	✓/✗	NS	✓	✓
[b]Martoni 2005[54]	NS	NS	✓	✓	NS	✓	✓
Thomas 2006[58]	NS	NS	✓	✓	✓/✗	✓	NS
Chen 2007[52]	NS	✓	✓	✓	✓	✓	✓
Helbekkmo 2007[55]	✓	✓	✓	✓	✓	✓	✓
Langer 2007[56]	✓	NS	✓	✓	NS	✓	NS
Ohe 2007[57]	✓	✓	✓	✓	NS	✓	✓
Chang 2008[50]	NS	NS	✓	✓	NS	✓	✓
Scagliotti 2008[61]	✓	NS	✓	✓	NS	✓	✓
Gronberg 2009[62]	NS	✓	✓	✓	NS	✓	✓
IPASS: Mok 2009[15] and Fukuoka 2011[64]	✓	✓	✓	✓	NS	✓	✓
Tan 2009[59]	✓	NS	✓	✓	NS	✓	✓
Maemondo 2010[63]	NS	✓	✓	✓	✓	✓	✓
Mitsudomi 2010[65]	✓	✓	✓	✓	NS	✓	✓
Treat 2010[60]	NS	NS	✓	✓	NS	✓	NS

✓, yes (item adequately addressed); ✗, no (item not adequately addressed); ✓/✗, partially (item partially addressed); IPASS, Iressa Pan ASian Study; NA, not applicable; NS, not stated.

a Where no *p*-values are reported the trial was assessed as NS.

b Second-line chemotherapy and/or palliative radiotherapy.

Blinding				Withdrawals			
Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	ITT	Other outcomes
NS	NS	NS	NS	✓	✓	✓	✓
NS	NS	NS	NS	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✗	✗
✗	✗	✗	NA	✓	✓	✓	✗
NS	NS	NS	NS	✓	✓	✓	✗
NS	NS	NS	NS	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✓	✗
NS	NS	NS	NS	✓	✓	✓	✓
NS	NS	NS	NS	✓	✓	✗	✗
✗	✗	✗	NA	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✓	✗
NS	NS	NS	NS	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✗	✓
NS	NS	NS	NS	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✓	✓
✗	✗	✗	NA	✓	✓	✗	✗
✗	✗	✗	NA	✓	✓	✓	✗
✓	✗	✗	NA	✓	✓	✓	✗
✓	NS	NS	NS	✓	✓	✗	✗
✗	✗	✗	NA	✓	✓	✗	✗
NS	NS	NS	NS	✓	✓	✓	✓

TABLE 10 Trial comparisons

Pair-wise comparison	Trials	Number of comparisons
GEM + PLAT vs VNB + PLAT	Chang 2008;[50] Gebbia 2003;[49] Gridelli 2003;[45] Helbekkmo 2007;[55] Martoni 2005;[54] Ohe 2007;[57] Scagliotti 2002;[43] and Thomas 2006[58]	8
GEM + PLAT vs PAX + PLAT	Langer 2007;[56] Ohe 2007;[57] Scagliotti 2002;[43] Schiller 2002;[47] Smit 2003;[46] and Treat 2010[60]	6
GEM + PLAT vs DOC + PLAT	Schiller 2002[47]	1
GEM + PLAT vs PEM + PLAT	Gronberg 2009;[62] and Scagliotti 2008[61]	2
VNB + PLAT vs PAX + PLAT	Chen 2004;[51] Kelly 2001;[48] Ohe 2007;[57] and Scagliotti 2002[43]	4
VNB + PLAT vs DOC + PLAT	Chen 2007;[52] Douillard 2005;[53] Fossella 2003;[44] and Tan 2009[59]	4
PAX + PLAT vs DOC + PLAT	Schiller 2002[47]	1
PAX + PLAT vs GEF	Maemondo 2010;[63] and IPASS[15,64]	2
DOC + PLAT vs GEF	Mitsudomi 2010[65]	1

IPASS, Iressa Pan ASian Study.

Doses of chemotherapy drugs used varied, the median number of chemotherapy cycles ranged from 2.6 to 6, and route of administration was intravenous (i.v.) or oral. The majority of trials reported second-line chemotherapy and/or palliative radiotherapy, with the exception of one trial[47] that reported that second-line treatment data were not collected, and four trials[49,56,58,65] in which it was unclear whether or not patients received any second-line treatment. Two trials[48,54] reported that patients who went on to have radiotherapy were excluded from the analysis.

Patient characteristics

Patient characteristics are presented in *Appendix 10*. Trial patients are generally younger and have better PS and fewer comorbidities than patients in a clinical setting. Full details of individual trial inclusion criteria can be found in *Appendix 11*. The majority of patients were male with adenocarcinoma stage IIIB or IV and a PS of 1. Only five trials[46,48,55,58,60] reported details of the staging system used to classify patients and given the variety in the dates and settings of the trials, the staging systems used is most likely to have varied across trials.

The number of patients randomised into trial arms ranged from 39 to 863. Median age ranged from 56 to 67 years within the clinical trials, which is younger than routinely found in clinical practice. The most common age group at diagnosis of 'malignant neoplasm of bronchus or lung' for men and women in England in 2008 was 75–79 years.[78] The percentage of males within each trial arm ranged from 56% to 84% for trials with PLAT-based doublets incorporating third-generation chemotherapy drugs. In the three GEF trials,[15,63–65] the proportion of males to females is much less; the percentage of males ranged from 21% to 37%, this is because sex is a factor in the likelihood of the presence of EGFR mutation (mutation found more often in females).

The patient populations in the trials by Maemondo *et al.*[63] and Mitsudomi *et al.*[65] were quite different from those in the other trials. These two trials[63,65] were based on molecular selection, and only patients with EGFR M+ tumours were eligible for inclusion. The Iressa Pan ASian Study (IPASS)[15,64] restricted the patient population to those with adenocarcinoma who were never-smokers or former light smokers in order to increase the likelihood of the presence of the EGFR mutation. All three trials[15,63–65] were multicentre, but conducted within East Asian countries. Patients assigned to the experimental arms received oral GEF at the standard dose (250 mg daily). Patients assigned to the chemotherapy arm received different PLAT-based doublets (PAX + CARB in two trials[15,63,64] and DOC + CIS in one trial[65]).

The majority of patients within the trials had stage IIIB or IV disease; at least twice as many patients had stage IV disease as stage IIIB disease.

Outcomes

Non-small cell lung cancer population with squamous disease

Eighteen trials are included for outcomes in this patient population; these 18 trials[43–60] reported outcomes in trials with mixed-patient populations (i.e. a mix of squamous and non-squamous disease). The results of these 18 trials are data available for patients with squamous disease and patients with non-squamous disease.

Median OS was reported in all 18 trials; two papers[43,44] also directly reported HR for OS. All 18 trials reported median PFS or TTP (as defined by each individual trial); one trial reported HRs for PFS[45] and one trial reported HRs for TTP.[43] Sixteen trials[43,44,46–57,59,60] reported survival rates at 1 year and nine trials[44,47,48,53–57,60] reported survival rates at 2 years. Sixteen trials[43,44,46–54,56–60] reported tumour ORR. Full details of the outcomes assessed in each trial are presented in *Table 11*.

Across the trials, median OS ranged from 6.2 to 15.4 months and median PFS/TTP ranged from 3.0 to 8.4 months. Definitions of PFS and TTP varied between trials and are reviewed in more detail in *Results of evidence synthesis*. Survival rates at 1 year ranged from 19.6% to 60.9% and at 2 years ranged from 7% to 31.5%. Tumour ORR ranged from 14% to 45.8%.

In terms of OS, one trial[44] demonstrated statistically significant differences between chemotherapy drug regimens; patients in the DOC + CIS arm had a significantly longer median OS than those in the VNB + CIS arm. However, the HR was not considered to be statistically significant.

In terms of PFS, two trials[47,51,61] demonstrated statistically significant differences between chemotherapy drug regimens. In one trial,[47] patients treated with GEM + CIS had a significantly longer median PFS than those on PAX + CIS (4.2 months compared with 3.4 months, respectively). In another trial,[51] patients treated with VNB + CIS had a significantly longer median PFS than patients treated with PAX + CIS (8.4 months compared with 6.0 months, respectively).

Two trials[44,49] showed statistically significant differences for tumour ORR; one trial[44] showed that DOC + CIS was associated with a beneficial partial response of the tumour compared with VNB + CIS and another trial[49] was associated with a beneficial partial response of the tumour to VNB + CIS compared with GEM + CIS.

Patients with non-squamous disease

The results of the 18 trials included in the NSCLC population with squamous disease are equally applicable for inclusion the NSCLC population with non-squamous disease. However, two additional trials[61,62] reported outcomes specifically in subgroups of patients with non-squamous disease. Details of the outcomes assessed in each trial are presented in *Table 12*.

In a trial by Scagliotti *et al.*[61] comparing PEM + CIS compared with GEM + CIS, OS was statistically significantly superior for patients with non-squamous disease who received PEM + CIS compared with GEM + CIS.

Another PEM trial[62] did not find any significant difference in survival when analysing patients with non-squamous disease separately ($n = 248$: PEM + CARB, 7.8 months; GEM + CARB, 7.5 months; $p = 0.77$).

Epidermal growth factor receptor mutation-positive population

Three trials were included: two trials[63,65] specifically included only patients with EGFR M+ status and in the third, the IPASS,[15,64] patients were selected in order to produce a relatively high proportion of patients with

TABLE 11 Outcomes, NSCLC population with squamous disease

		OS			PFS			Survival 1 year		Survival 2 years		Tumour ORR	
Trial	Treatment	Median, months	95% CI	HR (CI)	Median, months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	CI
Kelly 2001[48]	VNB + CIS	8.1	6.7 to 9.6	NR	4	NR	NR	36	NR	16	NR	28	NR
	PAX + CARB	8.6	7.2 to 10.7	NR	4	NR	NR	38	NR	15	NR	24	NR
Scagliotti 2002[43]	GEM + CIS	9.8	8.6 to 11.2	0.87 (95% CI 0.69 to 1.09)	5.3 (TTP)	4.4 to 6.3	0.95 (0.77 to 1.77)	37	NR	NR	NR	30	95% CI 24 to 37
	PAX + CARB	9.9	9.0 to 12.5	0.84 (95% CI 0.67 to 1.05)	5.5 (TTP)	4.6 to 6.4	0.91 (0.74 to 1.22)	43	NR	NR	NR	32	95% CI 25 to 38
	VNB + CIS	9.5	8.3 to 11.0	NR	4.6 (TTP)	3.9 to 5.6		37	NR	NR	NR	30	95% CI 24 to 36
Schiller 2002[47]	PAX + CIS	7.8	7.0 to 8.9	NR	3.4 (TTP)	2.8 to 3.9	NR	31	26 to 36	10	5 to 12	21	NR
	GEM + CIS	8.1	7.2 to 9.4	NR	4.2 (TTP), $p = 0.008$ vs PAX + CIS	3.7 to 4.8	NR	36	31 to 42	13	7 to 15	22	NR
	DOC + CIS	7.4	6.6 to 8.8	NR	3.7 (TTP)	2.9 to 4.2	NR	31	26 to 36	11	7 to 14	17	NR
	PAX + CARB	8.1	7.0 to 9.5	NR	3.1 (TTP)	2.8 to 3.9	NR	34	29 to 40	11	7 to 14	17	NR
[a]Fossella 2003[44]	DOC + CIS	11.3, $p = 0.044$ vs VNB + CIS	10.1 to 12.4	1.183 (97.2% CI 0.989 to 1.416)	5.07 (TTP)	4.84 to 5.76	NR	46	42 to 51	21	16 to 25	31.6, $p = 0.028$ vs VNB + CIS	95% CI 27.1 to 36.4
	DOC + CARB	9.4	8.7 to 10.6	1.048 (97.2% CI 0.877 to 1.253)	4.61 (TTP)	4.38 to 5.30	NR	38	33 to 43	18	13 to 22	23.9	95% CI 19.8 to 28.3
	VNB + CIS	10.1	9.2 to 11.3		5.30 (TTP)	4.84 to 6.22	NR	41	36 to 46	14	10 to 18	24.5	95% CI 20.4 to 29.0
Gebbia 2003[49]	GEM + CIS	8.2	NR	NR	4.0 (TTP)	NR	NR	24	NR	NR	NR	34	95% CI 26 to 42
	VNB + CIS	9.0	NR	NR	4.1 (TTP)	NR	NR	20	NR	NR	NR	44, $p = 0.032$ vs GEM + CIS	95% CI 36 to 53

Trial	Treatment	OS			PFS			Survival 1 year		Survival 2 years		Tumour ORR	
		Median, months	95% CI	HR (CI)	Median, months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	CI
[b]Gridelli 2003[45]	GEM + CIS	NR	NR	NR	NR	NR	0.91 (0.70 to 1.18)	NR	NR	NR	NR	NR	NR
	VNB + CIS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smit 2003[46]	PAX + CIS	8.1	6.2 to 9.9	NR	4.2	3.2 to 4.5	NR	35.9	28.4 to 43.4	NR	NR	31.8	95% CI 24.4 to 39.2
	GEM + CIS	8.9	7.8 to 10.5	NR	5.1	4.5 to 5.7	NR	33.1	25.8 to 40.4	NR	NR	36.8	95% CI 29.2 to 44.5
Chen 2004[51]	PAX + CIS	11.7	7.8 to 15.6	1.13 (95% CI 0.76 to 1.68)[c]	6	NR	NR	46.3	NR	NR	NR	38.6	95% CI 29.3 to 47.9
	VNB + CIS	15.4	13.9 to 16.8		8.4, $p = 0.0344$ vs PAX + CIS	NR	NR	60.9	NR	NR	NR	38.6	95% CI 29.3 to 47.9
[b]Douillard 2005[53]	DOC + CIS	8.3	NR	0.89 (95% CI 0.66 to 1.20)[c]	5 (TTP)	NR	NR	37	NR	17	NR	33.9	95% CI 25.4 to 43.3
	VNB + CIS	9	NR	NR	5 (TTP)	NR	NR	36	NR	10	NR	26.3	95% CI 18.6 to 35.2
Martoni 2005[54]	VNB + CIS	11	9.0 to 13.0	NR	5 (TTP)	4.0 to 6.0	NR	39.7	NR	13.7	NR	32.1	95% CI 24.5 to 40.5
	GEM + CIS	11	9.0 to 13.0	NR	5 (TTP)	4.0 to 6.0	NR	44.4	NR	16.6	NR	26.7	95% CI 19.5 to 35.1
Thomas 2006[58]	GEM + CARB	10.99	6.28 to 13.75		4.61 (TTP)	2.37 to 7.17	NR	NR	NR	NR	NR	19.6	95% CI 9.8 to 33.1
	VNB + CIS	10.0	6.45 to 12.93	1.05 (95% CI 0.67 to 1.66)[c]	4.87 (TTP)	3.88 to 6.91	NR	NR	NR	NR	NR	29.2	95% CI 17.0 to 44.1
Chen 2007[52]	VNB + CIS	13.8	9.7 to 17.8		6.3	4.4 to 8.2	NR	51.7	NR	NR	NR	45.8	95% CI 31.7 to 59.9
	DOC + CIS	13	5.4 to 20.6	0.99 (95% CI 0.58 to 1.69)[c]	4.7	3.9 to 5.4	NR	55.5	NR	NR	NR	43.5	95% CI 29.2 to 57.8

continued

TABLE 11 Outcomes, NSCLC population with squamous disease (*continued*)

		OS			PFS			Survival 1 year		Survival 2 years		Tumour ORR	
Trial	Treatment	Median, months	95% CI	HR (CI)	Median, months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	CI
Helbekkmo 2007[55]	VNB + CARB	7.3	NR	NR	NR	NR	NR	28	NR	7	NR	NR	NR
	GEM + CARB	6.4	NR	NR	NR	NR	NR	30	NR	7	NR	NR	NR
Langer 2007[56]	GEM + CARB	6.9	NR	NR	3.0	1.7 to 4.8	NR	25.5	13.1 to 38.0	13.0	3.3 to 22.0	23	90% CI 13.1 to 34.4
	PAX + CARB	6.2	NR	NR	3.5	2.6 to 6.0	NR	19.6	8.7 to 30.5	7.8	0.5 to 15.2	14	90% CI 6.4 to 23.4
Ohe 2007[57]	GEM + CIS	14.0	NR	NR	4.0	NR	NR	59.6	NR	31.5	NR	30.1	NR
	PAX + CARB	12.3	NR	NR	4.5	NR	NR	51.0	NR	25.5	NR	32.4	NR
	VNB + CIS	11.4	NR	NR	4.1	NR	NR	48.3	NR	21.4	NR	33.1	NR
Chang 2008[50]	VNB + CIS	9.0	NR	NR	5.3	4.7 to 8.5	NR	33.3	NR	NR	NR	31	95% CI 16 to 46
	GEM + CIS	12.9	NR	NR	6.6	5.2 to 7.6	NR	55.9	NR	NR	NR	38	95% CI 21 to 55
Tan 2009[59]	VNB + CIS	9.9	8.41 to 11.6	NR	4.9	4.44 to 5.95	NR	39.4	NR	NR	NR	27.4	95% CI 21.2 to 34.2
	DOC + CIS	9.8	8.8 to 11.5	NR	5.1	4.34 to 6.14	NR	40.9	NR	NR	NR	27.2	95% CI 21.0 to 34.2
Treat 2010[60]	GEM + CARB	7.9	7.1 to 9.2	NR	4.3 (TTP)	4.1 to 5.1	NR	33.9	29.1 to 38.7	11.5	8.1 to 14.9	25.3	95% CI 21.0 to 30.0
	PAX + CARB	8.7	7.7 to 9.9	NR	4.7 (TTP)	4.2 to 5.5	NR	35.6	30.7 to 40.4	13.3	9.7 to 16.9	29.8	95% CI 25.3 to 34.7

NR, not reported.

a Minor differences in the distribution of prognostic variables for the two independent comparisons (DOC + CIS vs VNB + CIS and DOC + CARB vs VNB + CIS) resulted in slightly different point estimates for the control group.

b All outcomes are after first-line and before commencement of second-line treatment.

c Obtained by contacting authors.

All trials in this table included mixed-patient populations; we've assumed that, for the purposes of analysis, the results apply to patients with squamous disease.

TABLE 12 Outcomes, NSCLC population with non-squamous disease

		OS			PFS			Survival 1 year		Survival 2 years		Tumour ORR	
Trial	Treatment	Median (months)	95% CI	HR (95% CI)	Median (months)	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	95% CI
Scagliotti 2008[61]	PEM + CIS	11.8	10.4 to13.2	0.81 (0.70 to 0.94); $p = 0.005$	5.3	4.8 to 5.7	0.90 (0.79 to1.02)	NR	NR	NR	NR	NR	NR
	GEM + CIS	10.4	9.6 to11.2		4.7	4.4 to 5.4		NR	NR	NR	NR	NR	NR
Gronberg 2009[62]	PEM + CARB	7.8	5.4 to 10.1	0.96 (0.75 to 1.23)[a]	NR	NR	NR	NR	NR	NR	NR	NR	NR
	GEM + CARB	7.5	6.0 to 9.4		NR	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported.

a Obtained from contacting author.

Results presented in this table relate to patients with non-squamous disease-only EGFR M+.

EGFR M+ status and reported outcomes by the subgroup of patients with EGFR M+ status. Details of the outcomes assessed in each trial are presented in *Table 13*.

During the production of this review, final results from the IPASS were published by Fukuoka *et al.*;[64] the IPASS had already been included in this review as Mok *et al*.[15] The PFS and ORR outcomes are derived from Mok *et al.*;[15] however, the OS results were immature and so mature OS outcomes are derived from Fukuoka *et al*.[64]

In terms of median OS, there was no significant difference between GEF and PAX + CARB in two trials[15,63,64] and there was no significant difference between GEF and DOC + CIS.[65] The three GEF trials[15,63–65] demonstrated a statistically significant benefit of GEF in terms of HR for PFS compared with PAX + CARB, and DOC + CIS.

In the subgroup of 261 patients in the IPASS[15,64] who were EGFR M+, median PFS was significantly longer among those who received GEF than among those who received PAX + CARB (HR = 0.48; 95% CI 0.36 to 0.64; $p < 0.001$). In the subgroup of 176 patients who were EGFR mutation negative (M–), PFS was significantly longer among those who received PAX + CARB (HR = 2.85; 95% CI 2.05 to 3.98; $p < 0.001$).

In the Maemondo *et al*. trial,[63] median PFS was significantly longer in the GEF group (10.8 months vs 5.4 months) than in the PAX + CARB group (HR = 0.30; 95% CI 0.22 to 0.41; $p < 0.001$); ORR was also higher in the GEF group (73.7% vs 30.7%; $p < 0.001$). However, median OS was not significantly different between the treatment arms.

In the Mitsudomi *et al*. trial,[65] PFS was significantly longer in the GEF group than in the DOC + CIS group, with a median PFS time of 9.2 (95% CI 8.0 to 13.9) months compared with 6.3 (95% CI 5.8 to 7.8) months and a HR of 0.489 (95% CI 0.34 to 0.71; log-rank $p < 0.0001$).

The three GEF trials[15,63–65] demonstrated a statistically significant benefit of GEF in terms of tumour ORR compared with PAX + CARB and DOC + CIS.

TABLE 13 Outcomes, NSCLC population with EGFR M+ status

		Median OS			Median PFS			Survival 1 year		Survival 2 years		Tumour ORR	
Trial	Treatment	Months	95% CI	HR (CI)	Months	95% CI	HR (CI)	%	CI	%	CI	%	CI
IPASS: Mok 2009[15] and Fukuoka 2011[64]	GEF	21.6	NR	1.00 (0.76 to 1.33); $p = 0.990$	9.5	NR	0.48 (0.36 to 0.64); $p < 0.001$	NR	NR	NR	NR	71.2; $p < 0.001$	NR
	PAX + CARB	21.9	NR		6.3	NR		NR	NR	NR	NR	47.3	NR
Maemondo 2010[63]	GEF	30.5	NR	0.80 (0.52 to 1.23)[a]	10.8	NR	0.30 (0.22 to 0.41); $p < 0.001$	NR	NR	61.4	NR	73.7; $p < 0.001$	NR
	PAX + CARB	23.6	NR	NR	5.4	NR	NR	NR	NR	46.7	NR	30.7	NR
Mitsudomi 2010[65]	GEF	30.9	24.1[b]	1.638 (0.75 to 3.58); $p = 0.211$	9.2	8.0 to 13.9	0.489 (0.336 to 0.710); $p < 0.0001$	NR	NR	NR	NR	62.1; $p < 0.0001$	NR
	DOC + CIS	Not reached	15.0[b]		6.3	5.8 to 7.8		NR	NR	NR	NR	32.2	NR

NR, not reported.

a Obtained by contacting author.

b Data immature, follow-up ongoing.

Data presented in this table relate to patients with EGFR M+ disease only.

Results of evidence synthesis

Twenty-three trials[15,43–65] were eligible for inclusion in the direct meta-analysis and mixed-treatment comparison analyses, with 11,428 randomised patients.

Eighteen trials[43–60] were included in the analyses of the NSCLC population with squamous disease and are included in meta-analysis 1 and mixed-treatment comparison 1. The same 18 trials plus subgroup data from the two PEM trials[61,62] were included in the analyses of the NSCLC population with non-squamous disease and are included in meta-analysis 1 and mixed-treatment comparison 1. Two highly selective trials[63,65] as well as the IPASS[15,64] with an EGFR M+-only subgroup were included in the analyses of the NSCLC population with EGFR M+ status.

Population 1: non-small cell lung cancer patients with squamous disease

Eighteen trials[43–60] were eligible for inclusion in the direct meta-analysis and mixed-treatment comparison analyses in the population with squamous disease with 7382 randomised patients. Comparisons between PLAT-based doublets incorporating third-generation chemotherapy drugs were available from 18 trials.[43–60] The characteristics of trials and patients included in these trials are described narratively in *Assessment of clinical effectiveness*. A summary of chemotherapy regimens showing treatment arms included in the evidence synthesis is presented in *Table 14*, and shows that the majority of trials ($n = 16$) had at least one treatment arm containing a CIS regimen; whereas, nine trials had at least one treatment arm containing a CARB regimen.

Seven trials[43,44,47,48,56–58] directly compared CIS and CARB when used in combination with one of the third-generation chemotherapy drugs. The non-PLAT-based chemotherapy arms from four trials[45,46,49,60] were excluded from all analyses because these treatments are not currently recommended by NICE in the first-line management of patients with advanced NSCLC in the UK.

TABLE 14 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on at least one of the outcomes of interest (OS and PFS)

Trials	GEM + CIS	VNB+CIS	PAX + CIS	DOC + CIS	GEM + CARB	VNB+CARB	PAX + CARB	DOC + CARB
Kelly 2001[48]		✗					✗	
Schiller 2002[47]	✗		✗	✗			✗	
Scagliotti 2002[43]	✗	✗					✗	
Fossella 2003[44]		✗		✗				✗
Gebbia 2003[49]	✗	✗						
Gridelli 2003[45]	✗	✗						
Smit 2003[46]	✗		✗					
Chen 2004[51]		✗	✗					
Douillard 2005[53]		✗		✗				
Martoni 2005[54]	✗	✗						
Chen 2007[52]		✗		✗				
Helbekkmo 2007[55]					✗	✗		
Langer 2007[56]	✗						✗	
Ohe 2007[57]	✗	✗					✗	
Thomas 2006[58]		✗			✗			
Chang 2008[50]	✗	✗						
Tan 2009[59]		✗		✗				
Treat 2010[60]					✗		✗	
Total trials	**9**	**13**	**3**	**5**	**3**	**1**	**6**	**1**

Overall survival

Overall survival was defined consistently across trials as the time from randomisation to death from any cause. The data points included in the direct meta-analysis and mixed-treatment comparison analyses for OS are presented in *Table 15* and six pair-wise comparisons are summarised in *Figure 5*. Analyses for OS were based on 18 trials[43–60] involving 7382 randomly assigned patients and 6081 deaths. The data sources for OS HRs used in the direct meta-analysis and mixed-treatment comparison analyses are also displayed in *Table 15*. This indicates that not all trials reported HRs for OS. Thus, pre-specified methods (see *Evidence synthesis*) were used to extract the HR and its variance for each trial that reported any information on OS outcome. The HRs for OS from three trials[43,44,57] were extracted directly from the trial papers, data from four trials[51–53,58] were obtained by contacting the investigators. In addition, HRs for four trials[45–47,50] were extracted from a systematic review[79] of the literature as the HRs were not reported in the primary trial publication (three out of four investigators of the primary trials were also co-authors of this systematic review). The remaining seven trials[48,49,54–56,59,60] did not report HRs for OS and could not be obtained from

TABLE 15 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on OS in the NSCLC population with squamous disease

Trials	Data source for HR and variance	GEM + PLAT	VNB + PLAT	PAX + PLAT	DOC + PLAT
Schiller 2002[47]	[a]Le Chevalier 2005[79]	✗		✗	✗
Kelly 2001[48]	Estimated HR from reported survival estimates using common approaches[66,67]		✗	✗	
Scagliotti 2002[43]	Published trial	✗	✗	✗	
Fossella 2003[44]	Published trial		✗		✗
Gebbia 2003[49]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗		
Gridelli 2003[45]	[a]Le Chevalier 2005[79]	✗	✗		
Smit 2003[46]	[a]Le Chevalier 2005[79]	✗		✗	
Chen 2004[51]	Author through e-mail		✗	✗	
Douillard 2005[53]	Author through e-mail		✗		✗
Martoni 2005[54]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗		
Chen 2007[52]	Author through e-mail		✗		✗
Helbekkmo 2007[55]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗		
Langer 2007[56]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗	
Ohe 2007[57]	Published trial	✗	✗	✗	
Thomas 2006[58]	Author through e-mail	✗	✗		
Chang 2008[50]	[a]Le Chevalier 2005[79]	✗	✗		
Tan 2009[59]	Estimated HR from reported survival estimates using common approaches[66,67]		✗		✗
Treat 2010[60]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗	
Total trials		**12**	**14**	**8**	**5**

a HRs extracted from systematic review by Le Chevalier 2005.[79]

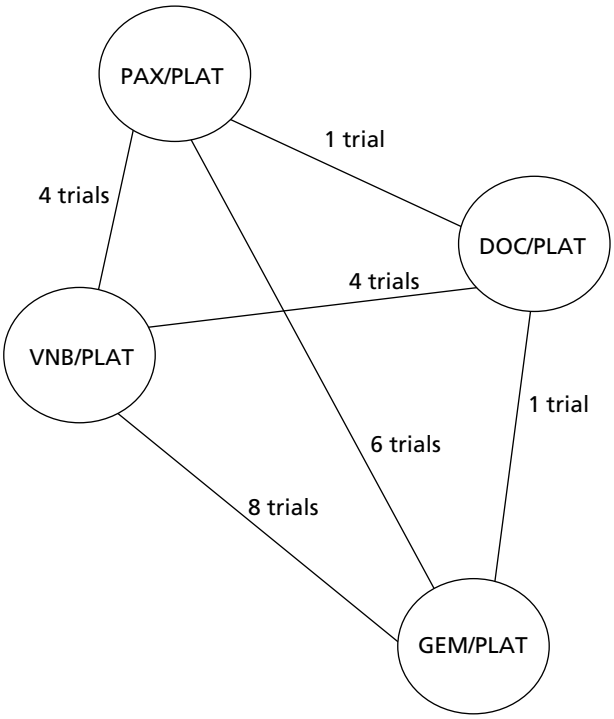

FIGURE 5 Network of RCTs comparing chemotherapy in the treatment of first-line advanced NSCLC (OS) for the mixed-treatment comparison and meta-analysis in the population with squamous disease.

trial authors. A network of 18 connected RCTs with six different treatment comparisons is presented in *Table 15* and *Figure 5*. The circles in *Figure 5* represent different treatments, and the lines represent direct head-to-head trials informing each comparison. Unconnected circles indicate a lack of direct randomised comparison.

Result summaries for all pair-wise comparisons between interventions from the direct meta-analysis and the mixed-treatment comparison primary analyses are presented in *Table 16*. Individual trial results and overall pooled results from both analyses, where available, are also displayed as forest plots for each pair-wise comparison. Results for the mixed-treatment comparison sensitivity analyses of OS are presented in *Appendix 12*.

Gemcitabine plus platinum compared with vinorelbine plus platinum

Eight head-to-head RCTs[43,45,49,50,54,55,57,58] were eligible for inclusion in the direct meta-analysis and mixed-treatment comparison for GEM + PLAT compared with VNB + PLAT, with 2152 randomised patients and 1702 deaths. Seven trials[43,45,49,50,54,57,58] used a CIS-based regimen in at least one treatment arm. CARB-based regimens were used in two trials, in one trial[55] comparing GEM + CARB with VNB + CARB and in another trial[58] comparing GEM + CARB with VNB + CIS.

The HR and 95% CI for each trial are displayed in *Figure 6* together with pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 6*, the chi-squared test for heterogeneity ($p = 0.972$), and the I^2-statistic (0%) all suggest very good consistency. The pooled OS estimate from meta-analysis 1 (HR = 1.08; 95% CI 0.98 to 1.20) shows a trend in favour of GEM + PLAT, and this was similar to, and consistent with, results of mixed-treatment comparison analyses (see *Table 16* and *Figure 6*). However, as the CI includes a HR of unity we cannot exclude the possibility of no evidence of difference between GEM + PLAT and VNB + PLAT. The median OS of GEM + PLAT ranged from 6.4 to 14 months compared with 7.3 to 11.4 months for VNB + PLAT, with smaller trials showing larger median OS than bigger trials.

TABLE 16 Summary results of direct meta-analysis and mixed-treatment comparison of OS in the NSCLC population with squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of events (deaths) in reference treatment/ comparator	Direct meta-analysis 1 ($n = 18$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 18$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57,58]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.09 (0.99 to 1.19)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.05 (0.96 to 1.15)
GEM + PLAT vs DOC + PLAT[47]	1	301/304	262/271	1.06 (0.89 to 1.28)	1.00 (0.88 to 1.13)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.96 (0.86 to 1.08)
VNB + PLAT vs DOC + PLAT[44,52,53,59]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.92 (0.81 to 1.03)
PAX + PLAT vs DOC + PLAT[47]	1	602/304	538/271	0.98 (0.76 to 1.27)	0.95 (0.82 to 1.10)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Gemcitabine plus platinum compared with paclitaxel plus platinum

Six head-to-head RCTs[43,46,47,56,57,60] were eligible under this comparison, with up to 2589 patients and 2239 deaths. In this comparison, GEM was most frequently combined with CIS;[43,46,47,56,57] only one trial[60] used the GEM + CARB combination. Five trials[43,47,56,57,60] evaluated the efficacy of PAX + CARB and two trials[46,47] evaluated PAX + CIS. One multiarm trial[47] evaluated efficacy for both PAX + CIS and PAX + CARB; however, in our analyses we excluded the PAX + CIS arm from this trial because of limited data points and included the PAX + CARB arm for both direct meta-analysis and mixed-treatment comparison analyses. A sensitivity analysis using PAX + CIS data produced similar results to the direct meta-analysis and the mixed-treatment comparison analyses (see *Appendix 12*). The HR and 95% CI for each trial are displayed in *Figure 7* together with pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 7*, the chi-squared test for heterogeneity ($p = 0.948$), and the I^2-statistic (0%) all suggest very good consistency. The pooled OS estimate from meta-analysis 1 (HR = 1.03; 95% CI 0.94 to 1.13) was not statistically significant, and this was similar to and consistent with results from meta-analysis 2 and mixed-treatment comparison analyses (see *Table 16* and *Figure 7*). The results provide insufficient evidence to support a difference in OS between GEM + PLAT and PAX + PLAT treatment. The median OS of GEM + PLAT-treated patients ranged from 6.2 to 14 months compared with 6.9 to 12.3 months in PAX + PLAT trials.

Gemcitabine plus platinum compared with docetaxel plus platinum

One single trial[47] provided direct evidence for GEM + PLAT vs DOC + PLAT with 605 patients and 533 deaths contributing to this comparison. The PLAT-based regimen was the same in both treatment arms, implying that results from this comparison can be treated as the efficacy between GEM + CIS compared with DOC + CIS. The HR and 95% CI from this trial are presented in *Table 16* together with the pooled HR estimates from the mixed-treatment comparison analyses.

The direct estimate for OS from this trial was not statistically significant (HR = 1.06; 95% CI 0.89 to 1.28). There is insufficient evidence of a difference between GEM + PLAT and DOC + PLAT in terms of survival improvement. The median survival of patients in the GEM + PLAT arm was 8.1 months compared with 7.4 months in the DOC + PLAT arm.

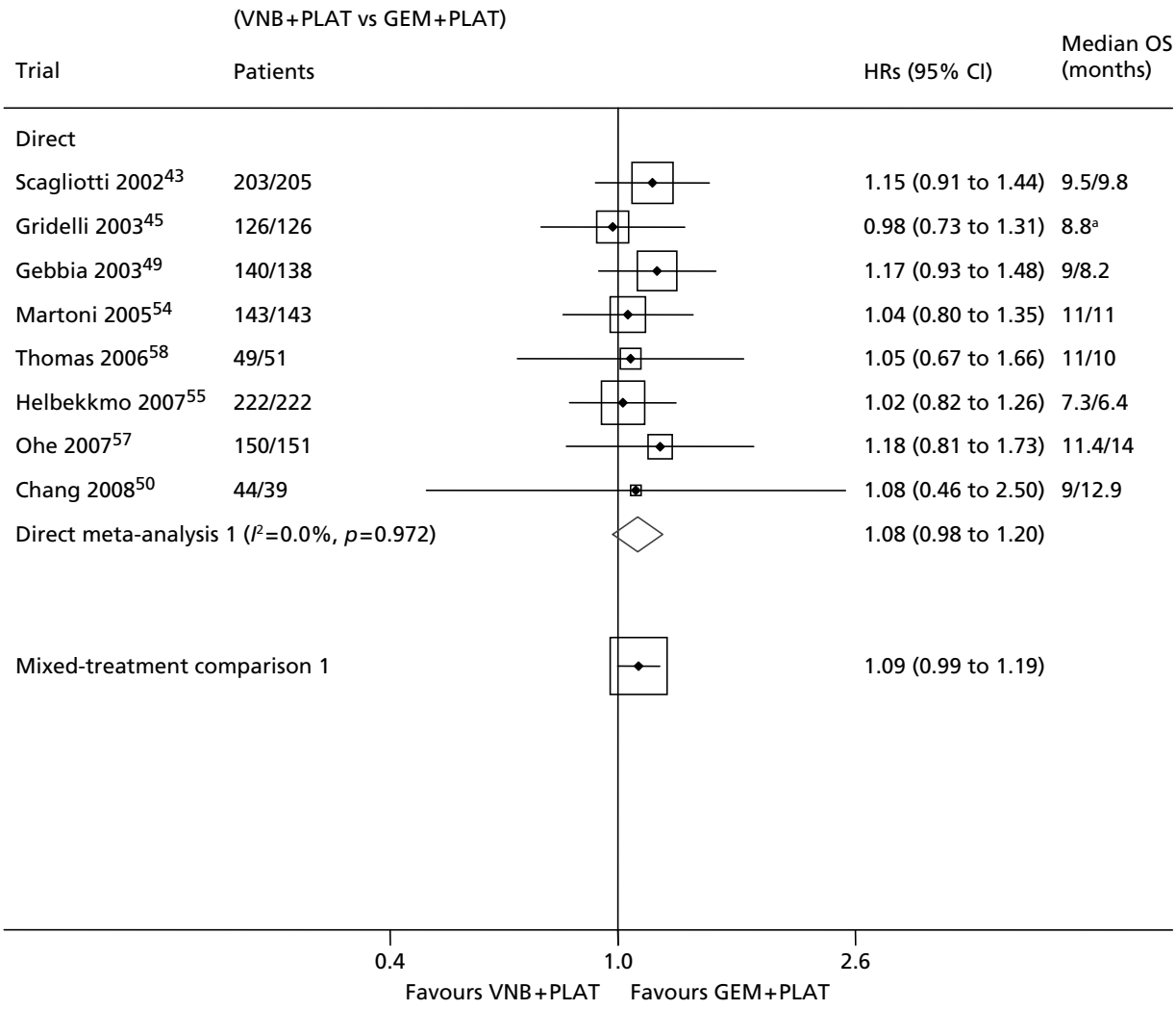

FIGURE 6 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing GEM + PLAT vs VNB + PLAT in the population with squamous disease. a, Same median OS reported for both treatment arms.

Vinorelbine plus platinum compared with paclitaxel plus platinum

Four head-to-head RCTs[43,48,51,57] were eligible for inclusion in this comparison, with 1228 patients and 977 deaths. CIS was used in combination with VNB in all trials; thus, the pooled results from this comparison can be treated as the efficacy of VNB + CIS. Three trials[43,48,57] evaluated the efficacy of PAX + CARB; only one trial[51] evaluated PAX + CIS.

The HR and 95% CI for individual trials are displayed in *Figure 8* together with the pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 8*, the chi-squared test for heterogeneity ($p = 0.802$), and the I^2-statistic (0%) all suggest very good consistency. The pooled OS estimate from meta-analysis 1 (HR = 0.98; 95% CI 0.83 to 1.16) was not statistically significant, and was similar and consistent with results from mixed-treatment comparison analyses (see *Figure 8*). Overall, these results provide insufficient evidence to support a difference in OS between VNB + PLAT and PAX + PLAT. Median OS associated with PAX + PLAT ranged from 8.6 to 12.3 months compared with 8.1 to 15.4 months in the VNB + PLAT trials (see *Figure 8*).

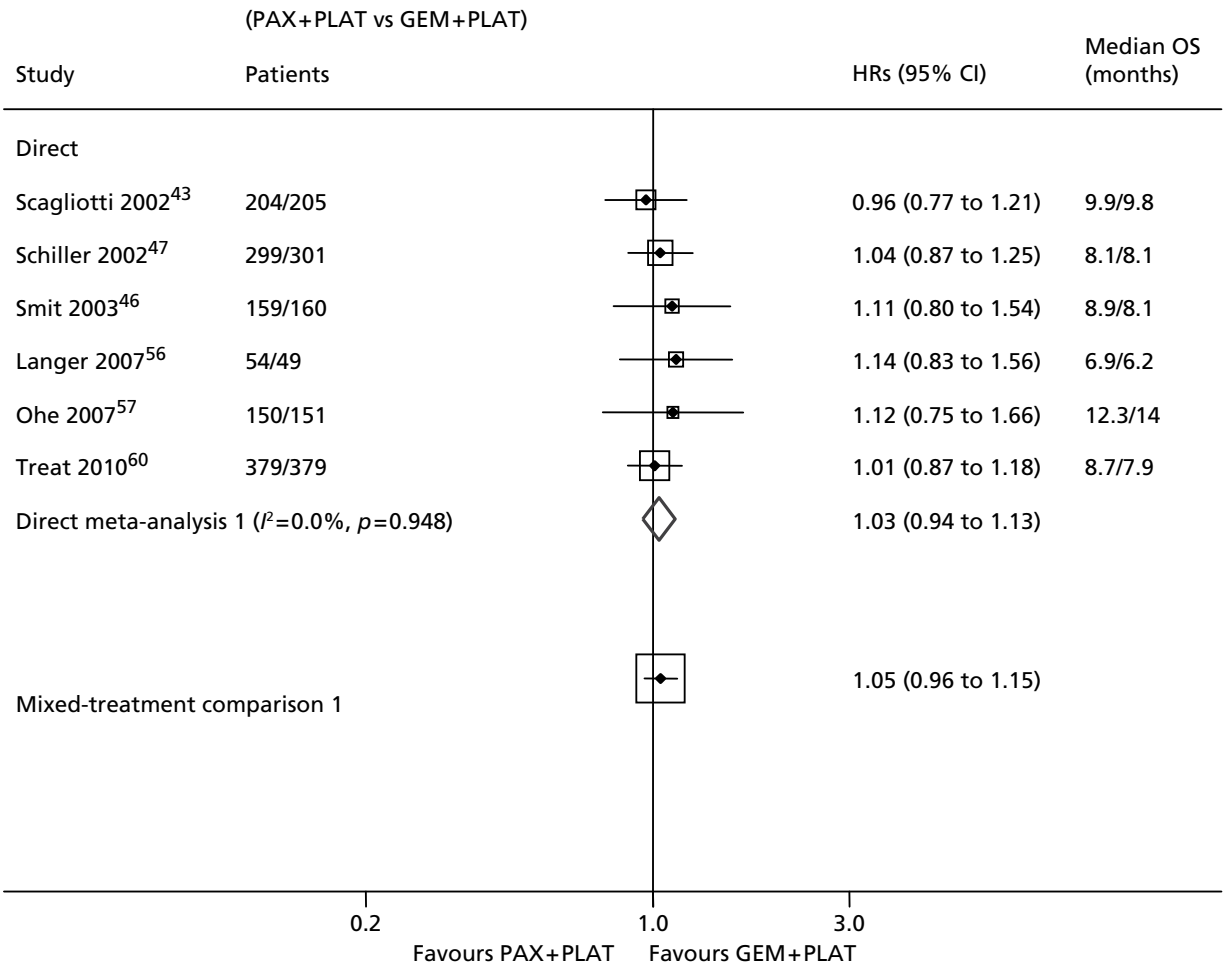

FIGURE 7 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing GEM + PLAT vs PAX + PLAT in the population with squamous disease.

Vinorelbine plus platinum compared with docetaxel plus platinum

Four head-to-head RCTs[44,52,53,59] were eligible for inclusion in this comparison, with 1525 patients and 1941 deaths. The PLAT regimen used in the four trials was CIS combined with VNB or DOC; thus, the pooled results from this comparison can be treated as the efficacy of VNB + CIS compared with DOC + CIS. One of these trials[44] also evaluated the efficacy of DOC + CARB in addition to two CIS-based arms; this arm was excluded from the analysis because of insufficient trial data on the DOC + CARB treatment combination. However, we tested the use of the DOC + CARB arm in a sensitivity analysis and the results of the analysis did not show any significant difference.

The HR and 95% CI for individual trials are displayed in the in *Figure 9* together with the pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 9*, the chi-squared test for heterogeneity ($p = 0.906$), and the I^2-statistic (0%) all suggest very good consistency. The pooled OS estimate from meta-analysis 1 (HR = 0.89; 95% CI 0.78 to 1.00) suggest an advantage to DOC + PLAT with similar and consistent results from mixed-treatment comparison analyses (see *Table 16* and *Figure 8*). However, the CI includes values of HR that may not be clinically important. Median OS for DOC + PLAT ranged from 8.3 to 13 months compared with 9 to 13.8 months in the VNB + PLAT trials (see *Figure 9*).

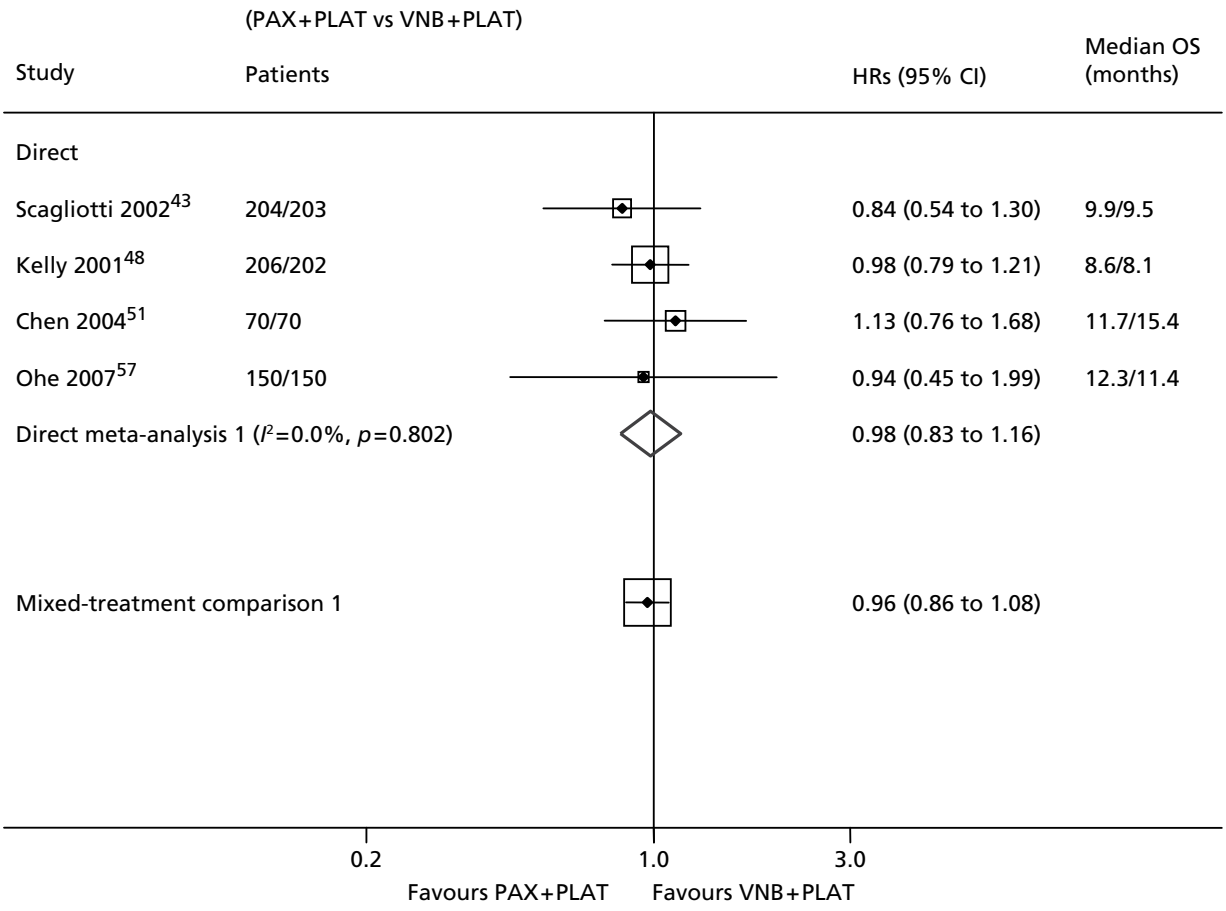

FIGURE 8 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing VNB + PLAT vs PAX + PLAT in the population with squamous disease.

Paclitaxel plus platinum compared with docetaxel plus platinum

One head-to-head RCT[47] was identified that compared PAX + PLAT and DOC + PLAT with 603 randomised patients and 537 deaths. There were two PAX treatment arms, one consisting of PAX + CIS and the other consisting of PAX + CARB. We used PAX + CARB throughout our analyses as this was the most frequently used combination across trials. The HR and 95% CI from this trial are presented in *Table 16* together with the pooled HR estimates from the mixed-treatment comparison analyses.

The direct OS HR and 95% CI from this trial was not statistically significant (HR = 1.02; 95% CI 0.79 to 1.32). These findings indicate insufficient evidence to suggest any difference between PAX + PLAT and DOC + PLAT in terms of survival improvement. The median OS estimates in the treatment arms were similar, with 8.1 months in the PAX + PLAT arm and 7.4 months in the DOC + PLAT arm.

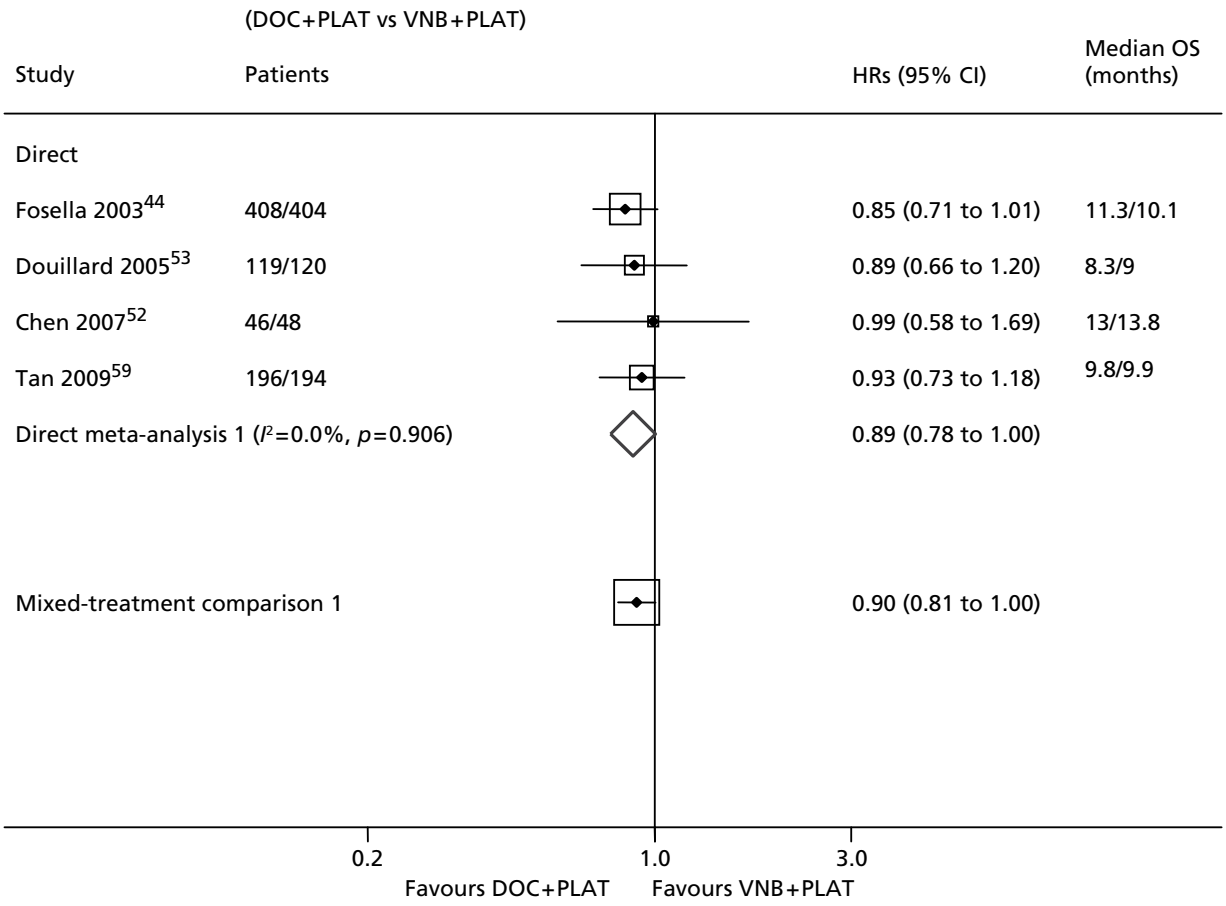

FIGURE 9 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing VNB + PLAT vs DOC + PLAT in the population with squamous disease.

Progression-free survival

The PFS and TTP outcomes in all of the 18 trials considered to be eligible for inclusion in the analysis of the population with squamous disease were reviewed. Eleven trials[43,44,46,48–50,55,57–60] were excluded from the PFS analysis since non-standard definitions of PFS appeared to be utilised by the investigators. Seven trials[45,47,51–54,56] were included in the PFS analysis detailed in *Table 17*; however, most of these trials used slightly different definitions of PFS. For instance, in six trials[45,47,51–54] PFS was referred to as TTP despite inclusion of death (as in the standard definition of PFS). This was particularly evident in trials designed before PFS was officially recognised as an appropriate surrogate for OS by the US FDA in 2007.[80]

A network of seven connected RCTs[45,47,51–54,56] with six different treatment comparisons is presented in *Table 18* and *Figure 10*. The circles in *Figure 10* represent different treatments, and the lines represent direct head-to-head trials informing each comparison. Unconnected circles indicate a lack of direct randomised comparison.

The data points included in the direct meta-analyses and mixed-treatment comparison analyses for PFS are presented in *Table 18* and six pair-wise comparisons are summarised in *Figure 10*. Analysis of PFS was based on seven trials involving 3523 patients.[45,47,51–54,56] The HRs for PFS for three trials[51–53] were obtained by contacting the investigators. Data from two trials[45,47] were extracted from a systematic review[79] as HRs were not reported in the primary trial publication (as noted earlier, three out of four investigators in the primary trials were also co-authors for this systematic review). The remaining two trials[54,56] did not report HRs for PFS and so the HRs and associated variance were extracted using information on PFS outcome by applying pre-specified methods[66,67] as described in *Evidence synthesis*.

TABLE 17 Definitions of PFS used in trials that were eligible for inclusion in the NSCLC population with squamous disease analysis

Trial	Trial definitions of PFS
Schiller 2002[47]	TTP was calculated from the date of enrolment to the date of progression or death
Gridelli 2003[45]	TTP was defined as the interval from date of random assignment to treatment and date of progression or death
Chen 2004[51]	TTP was calculated from the date of initiation of treatment to the date of disease progression or death
Douillard 2005[53]	TTP was defined as the time from random assignment to the first evidence of progressive disease or death
Martoni 2005[54]	TTP was defined as the time from random assignment to the first evidence of progressive disease or death, if progression was not documented
Chen 2007[52]	TTP was calculated from the date of initiation of treatment to the date of disease progression or death
Langer 2007[56]	PFS was defined as time from random assignment to tumour progression or death without documented disease progression

TABLE 18 Network of trials showing direct evidence for seven chemotherapy trials with ✗ reflecting available data on PFS in the population with squamous disease

Trials	Data source for HR and variance	GEM + PLAT	VNB + PLAT	PAX + PLAT	DOC + PLAT
Schiller 2002[47]	Le Chevalier 2005[79]	✗		✗	✗
Gridelli 2003[45]	Le Chevalier 2005[79]	✗	✗		
Chen 2004[51]	Author through e-mail		✗	✗	
Douillard 2005[53]	Author through e-mail		✗		✗
Martoni 2005[54]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗		
Chen 2007[52]	Author through e-mail		✗		✗
Langer 2007[56]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗	
Total trials		**4**	**5**	**3**	**3**

Table 19 shows pair-wise comparison results related to GEM + PLAT, VNB + PLAT, PAX + PLAT and DOC + PLAT from the direct meta-analyses and the mixed-treatment comparison analyses. Where appropriate, direct estimates for each included trial and overall pooled HRs from both sets of analyses are also displayed as forest plots within each pair-wise comparison section. Results for the mixed-treatment comparison sensitivity analyses of PFS are presented in *Appendix 13*.

Gemcitabine plus platinum compared with vinorelbine plus platinum

Two head-to-head RCTs[45,54] were eligible for this comparison, with 544 randomised patients. Both trials used CIS as the PLAT-based regimen; thus, this analysis can be considered as a comparison of GEM + CIS with VNB + CIS.

The HR and 95% CI for each trial are displayed in *Figure 11* together with the pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 11*, the chi-squared test for heterogeneity ($p = 0.943$), and the I^2-statistic (0%) all suggest very good consistency. The pooled PFS estimate from meta-analysis 1 (HR = 1.09; 95% CI 0.87 to 1.38) was not statistically significant, and was similar and consistent with results from mixed-treatment comparison analyses (see *Table 19* and *Figure 11*). These findings suggest lack of evidence to support any difference in PFS between GEM + CIS

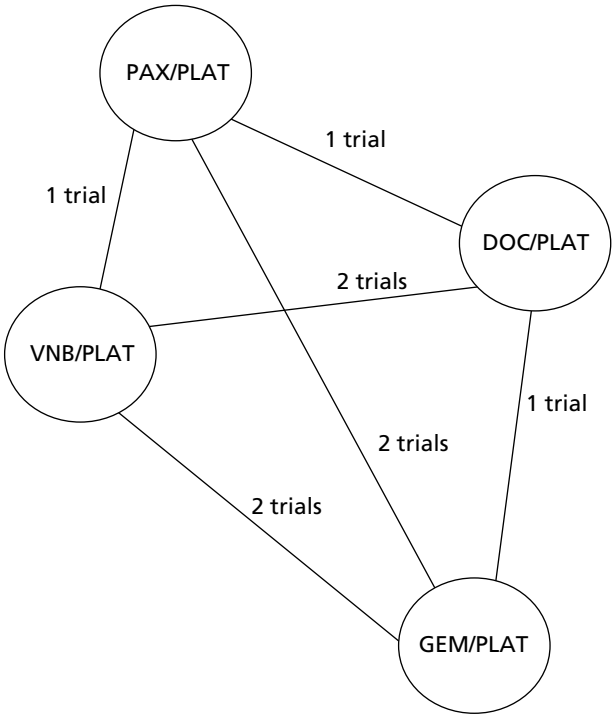

FIGURE 10 Network of RCTs comparing chemotherapy in the treatment of first-line advanced NSCLC PFS for the meta-analysis and mixed-treatment comparison analyses of the population with squamous disease. Total number of trials adds to nine because one trial[47] had more than one treatment arm.

TABLE 19 Summary results of direct meta-analysis and mixed-treatment comparison of PFS in the NSCLC population with squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of PFS events in reference treatment/ comparator	Direct meta-analysis 1 ($n = 9$), HR (95% CI)	Mixed-treatment comparison 1, HR ($n = 9$) (95% CI)
GEM + PLAT vs VNB + PLAT[45,54]	2	269/269	312[a]	1.09 (0.87 to 1.38)	1.06 (0.81 to 1.39)
GEM + PLAT vs PAX + PLAT[47,56]	2	350/656	142/304[b]	1.17 (1.00 to 1.36)	1.23 (0.94 to 1.62)
GEM + PLAT vs DOC + PLAT[47]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.79 to 1.45)
VNB + PLAT vs PAX + PLAT[51]	1	70/70	7/14[b]	**1.52 (1.06 to 2.17)**	1.16 (0.87 to 1.61)
VNB + PLAT vs DOC + PLAT[52,53]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.78 to 1.36)
PAX + PLAT vs DOC + PLAT[47]	1	602/304	130/263[b]	0.97 (0.75 to 1.24)	0.88 (0.62 to 1.21)

PD, progressive disease.

a In one trial, PFS events were reported for both arms.

b Includes progressive disease only as PFS event (PD or death) not reported.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Bold text indicates statistically significant result.

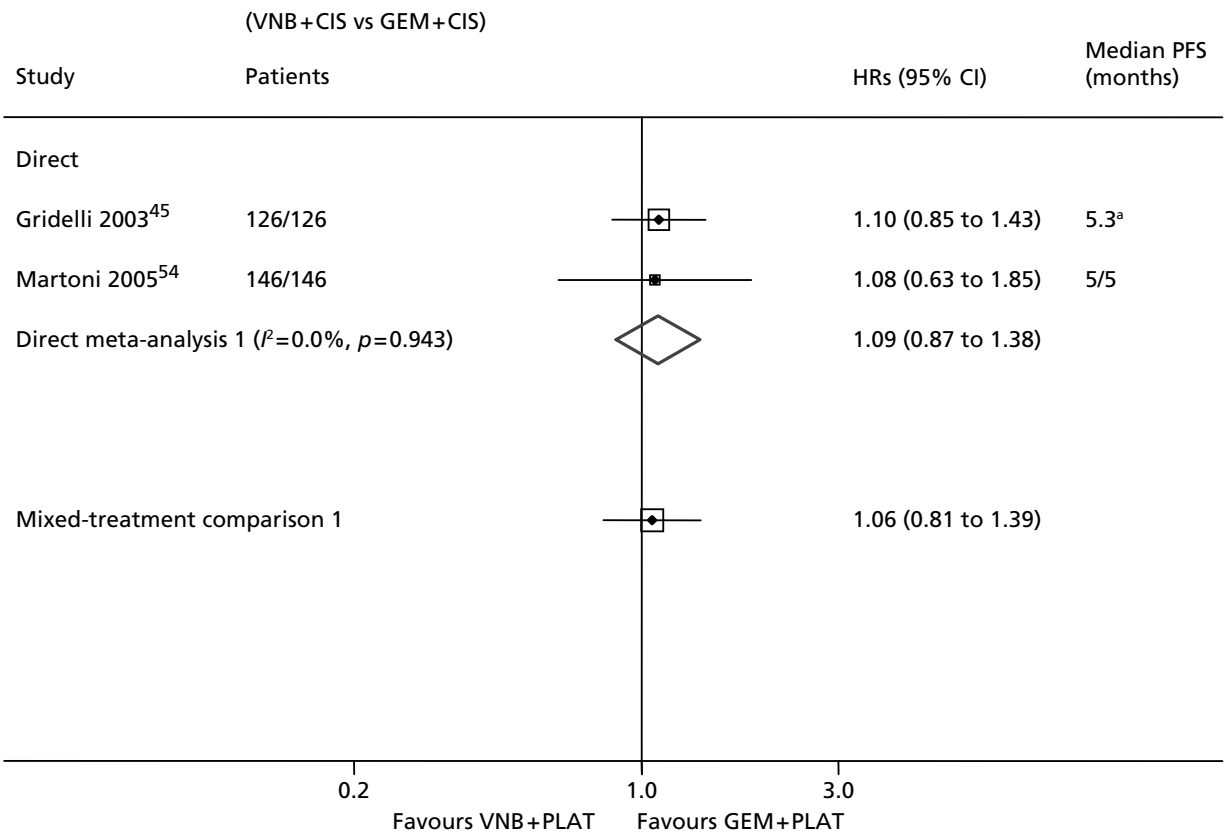

FIGURE 11 Forest plot illustrating results of meta-analysis 1 and mixed-treatment comparisons in terms of HRs and 95% CI for PFS in trials comparing GEM and VNB in combination with CIS in the population with squamous disease. a, Median PFS reported for both arms (5.3 months).

and VNB + CIS. Median PFS estimates were 5 months in both arms in one trial[54] and appear to be similar across the two trials.

Gemcitabine plus platinum compared with paclitaxel plus platinum

Two head-to-head RCTs[47,56] including 1001 patients contributed to this analysis. Both trials used CIS as the PLAT agent; thus, this analysis can be considered as a comparison of GEM + CIS with PAX + CIS. The HR and 95% CI for each trial are displayed in *Figure 12* together with the pooled result from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 12*, the non-significant chi-squared test for heterogeneity ($p = 0.670$), and the I^2-statistic (0%) all suggest very good consistency. The pooled direct HR (HR = 1.17; 95% CI 1.00 to 1.36; meta-analysis 1) suggests improvement in PFS for GEM + CIS over PAX + CIS, with a borderline statistically significant difference. The direct evidence is consistent with the results of the mixed-treatment comparison analyses. In addition, median PFS estimates were similar in both trials ranging from 3.0 to 4.2 months.

Gemcitabine plus platinum compared with docetaxel plus platinum

One single trial[40] provided direct evidence for GEM + PLAT compared with DOC + PLAT with 605 randomised patients and 219 PFS events contributing to this comparison. The PLAT-based regimen was the same in both arms (CIS); thus, this analysis can be considered as a comparison of GEM + CIS with DOC + CIS. The HR and 95% CI from this trial are presented in *Table 19* together with the pooled HR estimates from the mixed-treatment comparison analyses.

The direct PFS estimate from this trial was not statistically significant (HR = 1.15; 95% CI 0.96 to 1.37). This appears to be similar and consistent with the results from the mixed-treatment comparison analyses. The trial results and the findings from the mixed-treatment comparison analyses show insufficient

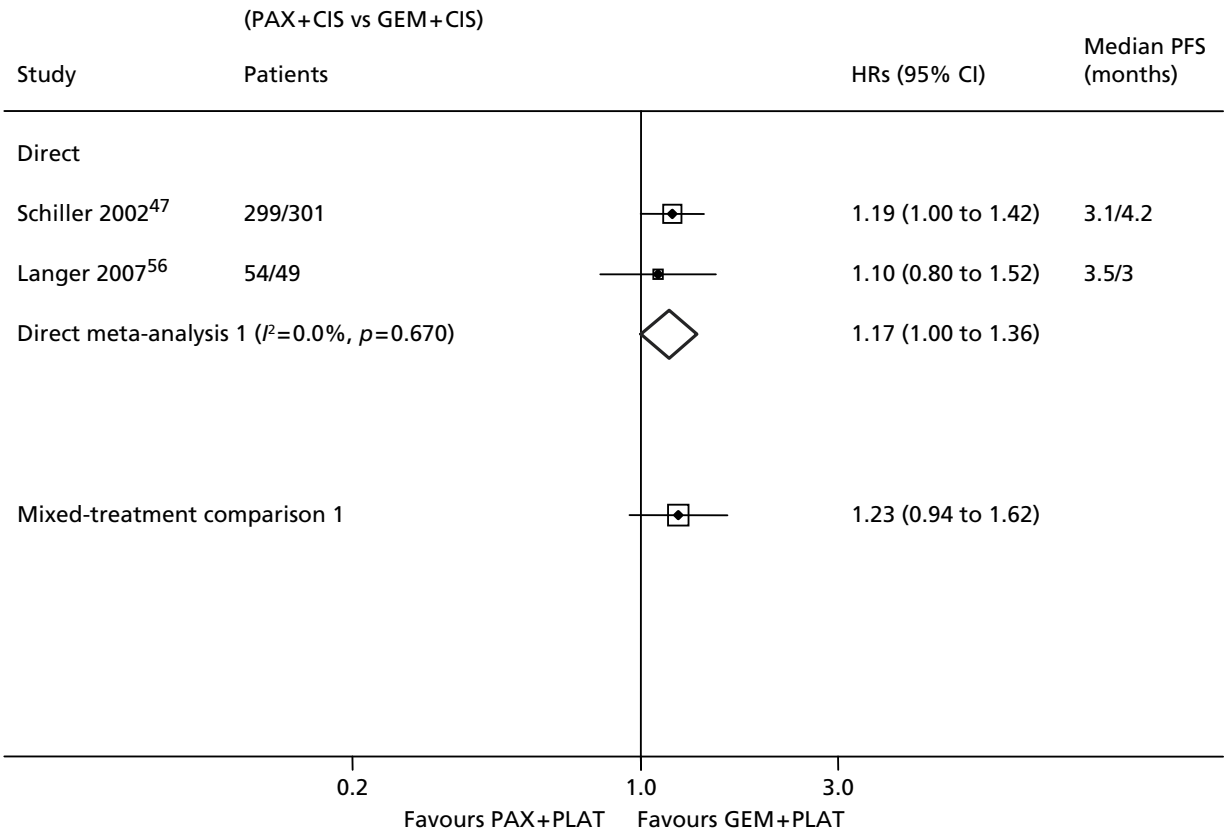

FIGURE 12 Forest plot illustrating results of direct meta-analysis and mixed-treatment comparison in terms of HRs and 95% CI of PFS in trials comparing GEM and PAX in combination with CIS in the population with squamous disease.

evidence to conclude whether or not there are differences in PFS between GEM + CIS and DOC + CIS. The median survival of patients in the GEM + CIS arm was 4.2 months compared with 3.7 months in the DOC + CIS arm.

Vinorelbine plus platinum compared with paclitaxel plus platinum

One single trial[51] provided direct evidence for VNB + PLAT compared with PAX + PLAT, with 140 randomised patients contributing to this comparison. The PLAT-based regimen was the same in both arms (CIS); thus, this analysis can be considered as a comparison of VNB + CIS vs PAX + CIS. The HR and 95% CI from this trial are presented in *Table 19* together with the pooled HR estimates from the mixed-treatment comparison analyses. The direct estimate of PFS HR from this trial was statistically significant (HR = 1.52; 95% CI 1.06 to 2.17), suggesting an advantage for VNB + CIS. However, although results from the mixed-treatment comparison analysis were consistent in direction of effect, the HR is pulled towards the null value by the dominating indirect evidence and the mixed-treatment comparison analysis is consequently not statistically significant. As the direct evidence comes from one small trial, these findings indicate a degree of uncertainty about the difference between VNB + CIS and PAX + CIS. The median PFS estimate was 8.4 months in the VNB + CIS arm and 6 months in the PAX + CIS arm.

Vinorelbine plus platinum compared with docetaxel plus platinum

Two trials[52,53] involving 333 patients explored the role of VNB + PLAT compared with DOC + PLAT. Both trials used CIS; thus, this analysis can be considered as a comparison of VNB + CIS with DOC + CIS. The HR and 95% CI from each trial are displayed in *Figure 13* together with the pooled HR estimates from meta-analysis 1 and the mixed-treatment comparison analyses. Visual examination of *Figure 13*, the non-significant chi-squared test for heterogeneity (p = 445) and the I^2-statistic (0%) all suggest very good consistency. PFS appeared favourable to DOC + CIS over VNB + CIS, although this was not statistically

significant (HR = 0.92; 95% CI 0.74 to 1.16). Similar findings were observed in the mixed-treatment comparison analyses (see *Table 19* and *Figure 13*). These results indicate insufficient evidence to conclude whether or not there are differences in PFS between VNB + CIS and DOC + CIS. Median PFS estimates in both arms were similar and ranged from 5 to 6.3 months in the VNB arms and 4.7 to 5 months in the DOC arms.

Paclitaxel plus platinum compared with docetaxel plus platinum

One single trial[47] provided direct evidence for PAX + PLAT compared with DOC + PLAT, with 906 randomised patients contributing to this comparison. The PLAT-based regimen was the same in both arms (CIS); thus, this analysis can be considered as a comparison of PAX + CIS with DOC + CIS. The HR and 95% CI from this trial are presented in *Table 19* together with the pooled HR estimates from mixed-treatment comparison analyses. There is insufficient evidence to conclude whether or not there are differences in PFS between PAX + CIS and DOC + CIS (HR = 0.97; 95% CI 0.75 to 1.24). We observed similar results in the mixed-treatment comparison analyses (see *Table 19*).

Time to disease progression

Time to disease progression was reported in 7 out of 21 trials.[43,44,46,49,50,58,60] Time to disease progression in RCTs is usually defined as the time from randomisation until objective tumour progression, and does not include death from other causes. We allowed these seven trials to be analysed as a group as their definitions of TTP were similar (*Table 20*).

The data points included in the direct meta-analysis and mixed-treatment comparison analyses for TTP are presented in *Table 21*. Analyses of TTP were based on outcomes for 3572 randomised patients and approximately 1258 progressive events. Data on log-HR and its variance from two trials[43,44] were extracted

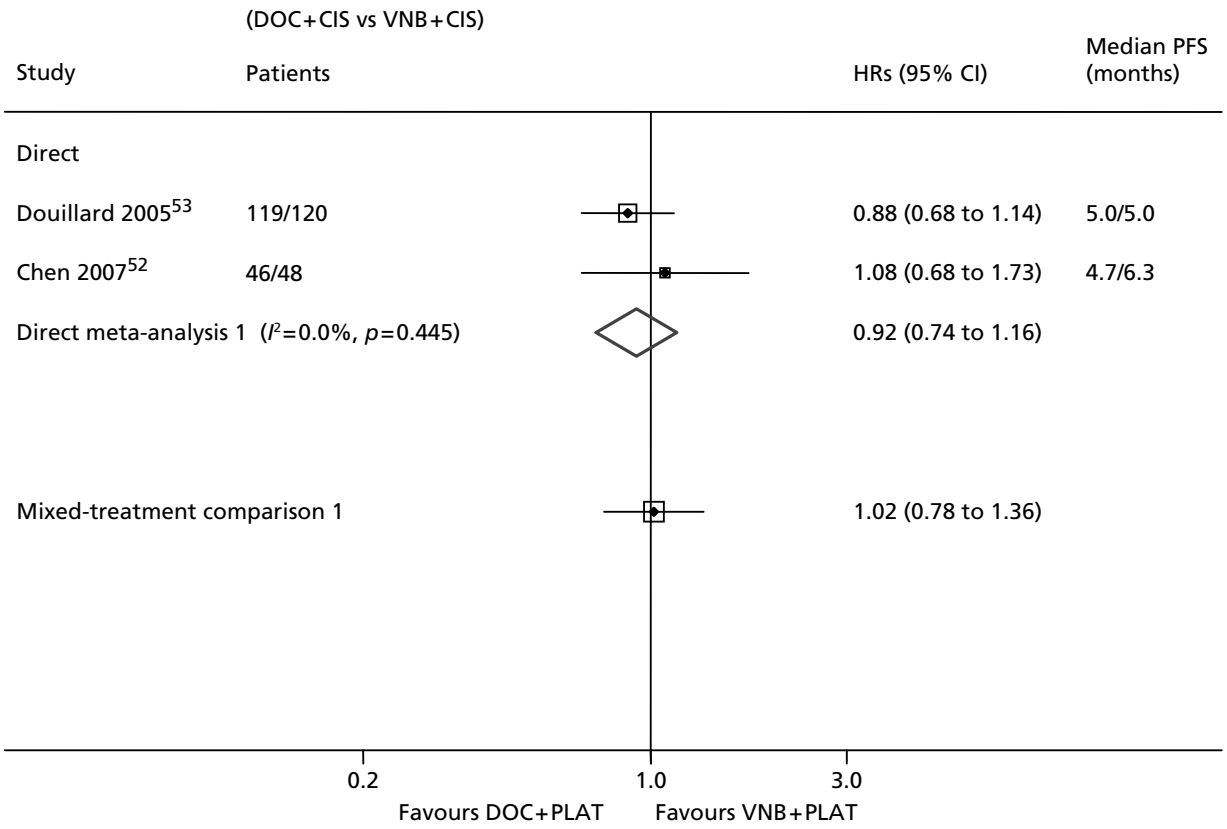

FIGURE 13 Forest plot illustrating results of direct meta-analysis and mixed-treatment comparison in terms of HRs and 95% CI of PFS in trials comparing DOC and VNB in combination with PLAT in the population with squamous disease.

TABLE 20 Definitions of TTP in the included trials for TTP analysis of the population with squamous disease

Trial	Trial definition of TTP
Scagliotti 2002[43]	TTP defined as interval between trial enrolment and progressive disease
Gebbia 2003[49]	TTP was calculated as the time elapsed from the date of patient's registration until the date of progressive disease or last documented control
Smit 2003[46]	Duration of survival and PFS were calculated from the date of randomisation to progression
Fossella 2003[44]	TTP was defined as the time from random assignment to first documentation of progressive disease
Thomas 2006[58]	TTP was measured from the date of first treatment administration until the time of progressive disease or relapse
Chang 2008[50]	TTP was calculated for all patients from the date of randomisation until the date progressive disease was first reported
Treat 2010[60]	TTP were assessed using the calculated from the date of randomisation to the date of documented progression

TABLE 21 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on TTP in the population with squamous disease

Trials	Data source for HR and variance	GEM + PLAT	VNB + PLAT	PAX + PLAT	DOC + PLAT
Scagliotti 2002[43]	Extracted from the published report	✗	✗	✗	
Gebbia 2003[49]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗		
Smit 2003[46]	Le Chevalier 2005[79]	✗		✗	
Fossella 2003[44]	Extracted from the published report		✗		✗
Thomas 2006[58]	Author through e-mail	✗	✗		
Chang 2008[50]	Author through e-mail	✗	✗		
Treat 2010[60]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗	
Number of trials for TTP analysis		**6**	**5**	**3**	**1**

directly from the published trials, data from two trials were obtained by contacting investigators[50,58] and data from one trial[46] were extracted from a previously published meta-analysis.[79] Two out of seven trials did not report HRs for TTP[49,60] and these were estimated via the pre-specified approaches[66,67] described in *Evidence synthesis*.

The network of comparisons for TTP showing seven connected RCTs[43,44,46,49,50,58,60] with six different treatment comparisons are presented in *Table 22* and *Figure 14*. The nodes in *Figure 14* represent different treatments and the lines represent direct head-to-head trials informing each comparison. Unconnected nodes indicate lack of direct evidence. The data overview indicate that PLAT-based doublets incorporating GEM, VNB, PAX and DOC generally had at least one data point and had been compared against each other.

Table 23 shows pair-wise comparison results between GEM + PLAT, VNB + PLAT, PAX + PLAT and DOC + PLAT from the direct meta-analyses and the mixed-treatment comparison analyses. Direct estimates for each included trial and overall pooled HR from both analyses are also displayed as forest plots within each pair-wise comparison section. Results for the mixed-treatment comparison sensitivity analyses of TTP are presented in *Appendix 14*. *Appendix 15* shows results for the mixed-treatment comparison sensitivity analyses of PFS and TTP combined.

TABLE 22 Trials included for each TTP pair-wise comparison in the population with squamous disease

Pair-wise comparison (reference treatment/comparator)	Number of patients in reference treatment/comparator	Number of events (TTP) reference treatment/ comparator	Number of data points
GEM + PLAT vs VNB + PLAT[43,49,50,58]	433/436	91/82	4
GEM + PLAT vs PAX + PLAT[43,46,60]	744/742	417/423	3
GEM + PLAT vs DOC + PLAT	XX	XX	0
VNB + PLAT vs PAX + PLAT[43]	203/204	34/37	1
VNB + PLAT vs DOC + PLAT[44]	404/406	86/88	1
PAX + PLAT vs DOC + PLAT	XX	XX	0
Total	**3572**	**1258**	

NR, not reported; XX, no direct evidence.

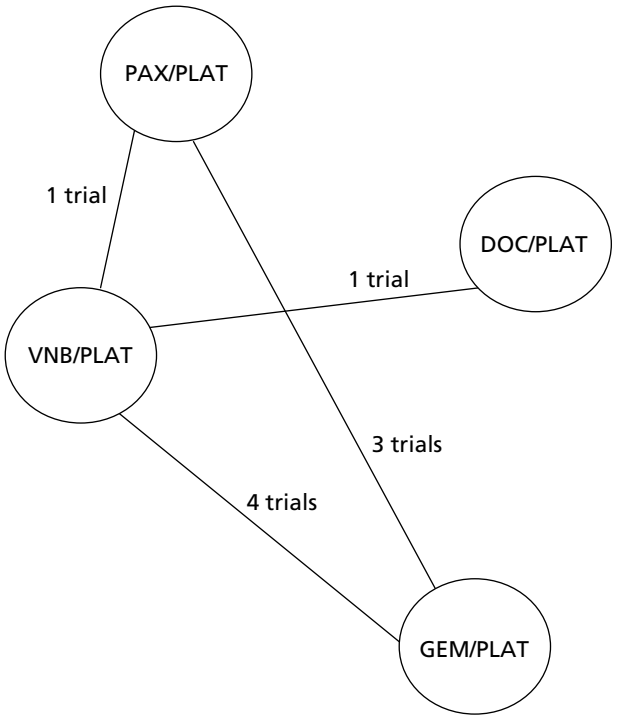

FIGURE 14 Network of RCTs comparing chemotherapy in the treatment of first-line advanced NSCLC TTP for the meta-analysis and mixed-treatment comparison analyses of the population with squamous disease. Total number of trials adds to nine because one trial[43] had more than one treatment comparator.

Gemcitabine plus platinum compared with vinorelbine plus platinum

Four head-to-head RCTs[43,49,50,58] were eligible under this comparison with 869 randomised patients. The PLAT-based regimen for VNB combination in all trials was CIS. For the GEM combination, one trial[58] had CARB as the PLAT-based regimen. The HR and 95% CI for each trial are displayed in *Figure 15* together with the pooled results from meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 15*, the chi-squared test for heterogeneity ($p = 0.992$) and the I^2-statistic (0%) all suggest very good consistency. The pooled TTP estimates from meta-analysis 1 (HR = 1.03; 95% CI 0.90 to 1.18) were not statistically significant, and this was similar and consistent with results from mixed-treatment comparison analyses (see *Table 23* and *Figure 15*). The estimated point estimate for the

TABLE 23 Summary results of direct meta-analysis and mixed-treatment comparison for TTP in NSCLC population with squamous disease

Reference treatment vs comparator	Number of data points	Number of patients in reference treatment/ comparator	Number of events (TTP) reference treatment/ comparator	Direct meta-analysis 1 ($n = 7$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 7$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,49,50,58]	4	433/436	91[a]/82[a]	1.03 (0.90 to 1.18)	1.02 (0.83 to 1.25)
GEM + PLAT vs PAX + PLAT[43,46,60]	3	744/742	417[a]/423[a]	1.01 (0.90 to 1.13)	1.21 (0.73 to 1.99
GEM + PLAT vs DOC + PLAT	0	XX	XX	XX	0.98 (0.62 to 1.52)
VNB + PLAT vs PAX + PLAT[43]	1	203/204	34[a]/37[a]	0.90 (0.64 to 1.28)[b]	0.99 (0.77 to 1.28)
VNB + PLAT vs DOC + PLAT[44]	1	404/406	86[a]/88[a]	0.96 (0.70 to 1.31)[b]	0.96 (0.65 to 1.43)
PAX + PLAT vs DOC + PLAT	0	XX	XX	XX	0.98 (0.6 to 1.55)

XX, no direct meta-analysis evidence.

a Includes progressive disease only as TTP events not reported.

b Direct evidence.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

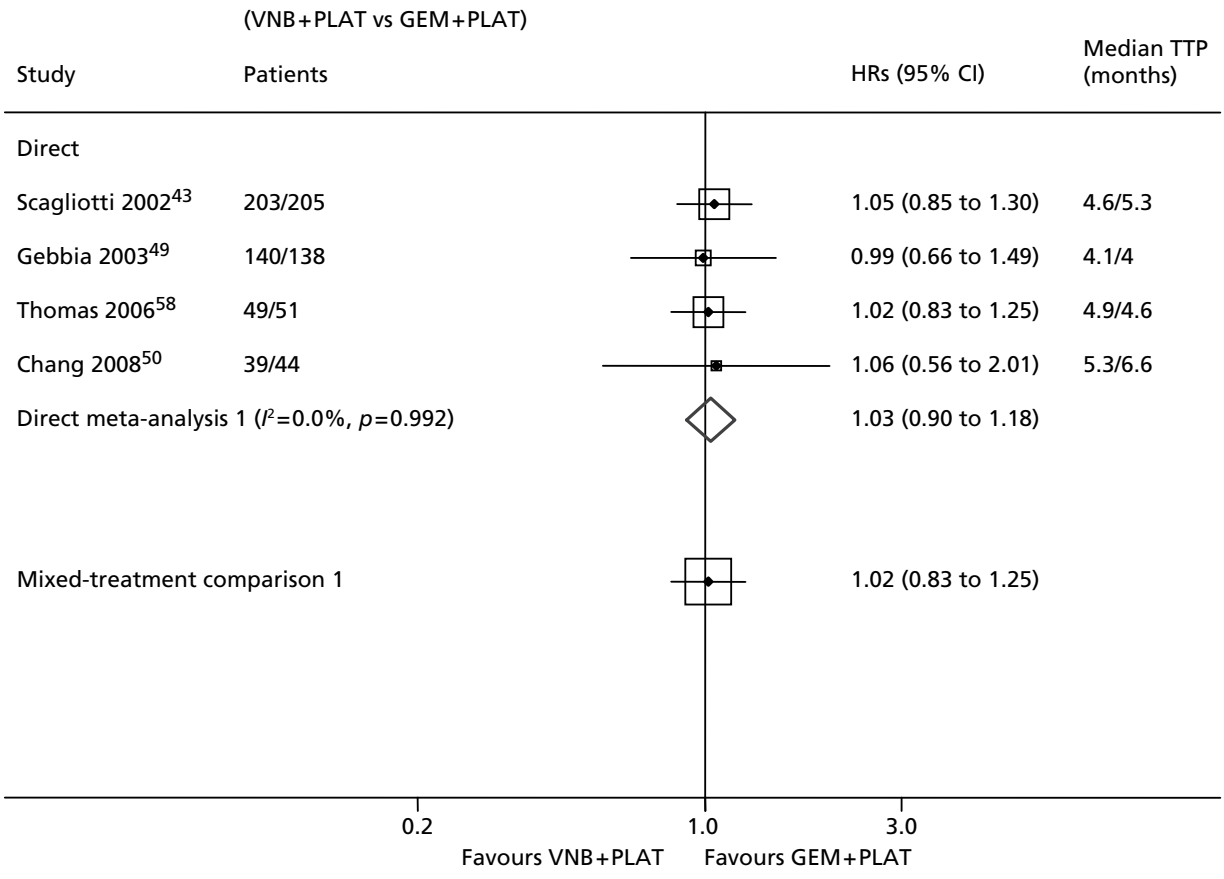

FIGURE 15 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison 1 in terms of HRs and 95% CI of TTP in trials comparing GEM and VNB in combination with PLAT in the population with squamous disease.

TTP HR was slightly different but also consistent with results from meta-analysis 1 and mixed-treatment comparison analyses. These results suggest that there is no evidence to support any difference in TTP between GEM + PLAT and VNB + PLAT. Median TTP estimates ranged from 4.1 to 5.3 months and 4 to 6.6 months in the VNB + PLAT and GEM + PLAT arms, respectively (see *Figure 15*).

Gemcitabine plus platinum compared with paclitaxel plus platinum

Three head-to-head RCTs PLAT[43,46,60] including 1486 patients contributed to this analysis. The treatment arm PLAT combinations used in the trials were not very common among the included trials. For instance, GEM + CIS was used in two trials,[43,46] GEM + CARB in one trial,[60] PAX + CIS in one trial[46] and PAX + CARB in two trials.[43,60] The HR and 95% CI for each trial are displayed in *Figure 16* together with the pooled meta-analysis 1 result and HRs from the mixed-treatment comparison analyses. Visual examination of *Figure 16*, the non-significant chi-squared test for heterogeneity ($p = 0.691$) and the I^2-statistic (0%) all suggest very good consistency. The pooled TTP estimate from the meta-analysis 1 (HR = 1.01; 95% CI 0.90 to 1.13) was not statistically significant, and this was slightly different but consistent with result from mixed-treatment comparison 1 analysis (see *Table 19*). These results suggest there is no evidence to support any difference in TTP between GEM + PLAT and PAX + PLAT. Median TTP estimates ranged from 4.3 to 5.3 months and 4.2 to 5.5 months in the GEM + PLAT and PAX + PLAT arms, respectively (see *Table 19* and *Figure 16*).

Gemcitabine plus platinum compared with docetaxel plus platinum

There was no trial that directly compared GEM + PLAT and DOC + PLAT and reported TTP outcome. Therefore, TTP comparison between these two drugs was based entirely on results from the mixed-treatment comparison analyses. Results from the mixed-treatment comparison analyses showed no significant difference in TTP between GEM + PLAT and DOC + PLAT (HR = 0.98; 95% CI 0.62 to 1.57;

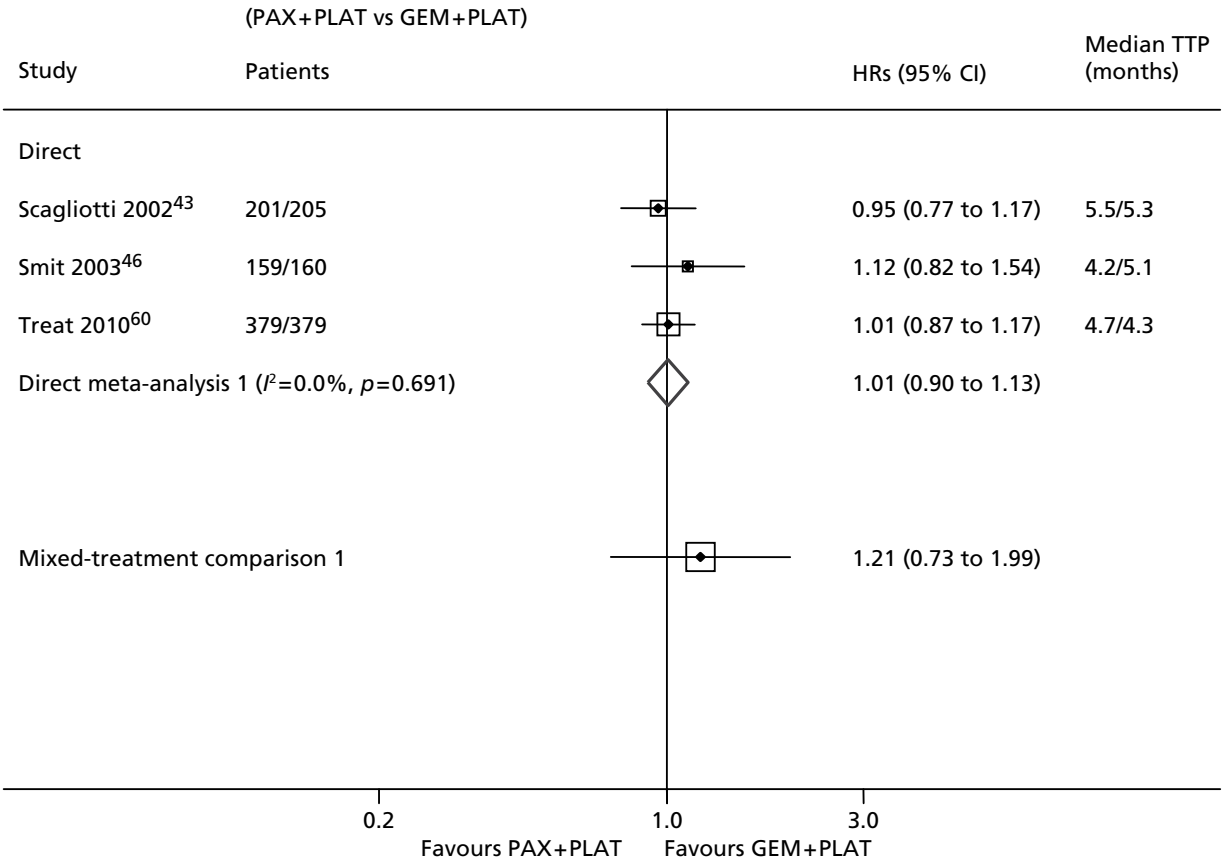

FIGURE 16 Forest plot illustrating results of direct meta-analysis 1 and mixed-treatment comparison 1 in terms of HRs and 95% CI of TTP in trials comparing GEM and PAX in combination with PLAT.

mixed-treatment comparison A). These findings, therefore, indicate insufficient evidence to conclude whether or not there are differences in TTP between GEM + PLAT and DOC + PLAT.

Vinorelbine plus platinum compared with paclitaxel plus platinum

There was one trial[43] that directly compared VNB + PLAT and PAX + PLAT, with 407 randomised patients contributing to this comparison. The PLAT-based regimens were different in the two treatment arms (VNB + CIS vs PAX + CARB). The HR and 95% CI from this trial are presented in *Table 23* together with the pooled HR estimates from the mixed-treatment comparison analyses. The direct HR estimate for TTP from this trial was 0.90 (95% CI 0.64 to 1.28) and was not statistically significant. The direct evidence appears to be slightly different from the mixed-treatment comparison results where the HRs were estimated at 0.99 (see *Table 23*). These findings indicate insufficient evidence to conclude whether or not there are differences in TTP between VNB + PLAT and PAX + PLAT. The median TTP estimates were similar between the treatment arms, with 4.6 months for patients in the VNB + PLAT arm compared with 5.5 months in the PAX + PLAT arm.

Vinorelbine plus platinum compared with docetaxel plus platinum

One trial[44] involving 810 patients and 174 TTP events explored the role of VNB + PLAT compared with DOC + PLAT and reported TTP. This was a multiarm trial with three treatment arms in which DOC was used in combination with either CIS or CARB. VNB was used in combination with CIS. The combination of DOC + CARB was used in the presented main analyses; however, inclusion of the DOC + CIS arm showed similar results (not presented). The direct HR and 95% CI estimates for the TTP from this trial were not statistically significant (HR = 0.96; 95% CI 0.70 to 1.31). The direct evidence was similar and consistent with the mixed-treatment comparison results as shown in *Table 23*. These results indicate insufficient evidence to conclude whether or not there are differences in TTP between VNB + PLAT and DOC + PLAT. Median TTP in both arms was similar (approximately 5 months).

Paclitaxel plus platinum compared with docetaxel plus platinum

There was no trial that directly compared PAX + PLAT and DOC + PLAT. Therefore, TTP comparison between these two drugs was based entirely on results from the mixed-treatment comparison analyses. The results from the mixed-treatment comparison analyses showed no significant difference in TTP between PAX + PLAT and DOC + PLAT (HR = 0.98; 95% CI 0.60 to 1.55; mixed-treatment comparison A); this result was consistent across the mixed-treatment comparisons. These findings indicate insufficient evidence to conclude whether or not there are differences in TTP between PAX + PLAT and DOC + PLAT.

Survival risk at year 1 and year 2 post randomisation

Year 1 and year 2 survival risk were defined as the probability of survival in intervals of time elapsed from randomisation to year 1 and year 2, respectively. Analyses were based on 17 trials[43,44,46–60] involving 7136 randomly assigned patients. There was insufficient information on survival risk at 1 or 2 years for one trial.[45] The proportion of patients still alive or survival rates at year 1 or 2 for all trials were extracted directly from the published reports or indirectly from the survival curves in the published reports.

Results for meta-analysis and mixed-treatment comparison analyses for 1-year and 2-year survival are shown in *Appendices 16* and *17,* respectively. Analyses for 1-year survival show no evidence to suggest any difference in survival between the third-generation chemotherapy treatments. None of the results from the 2-year analyses were statistically significant with wide CIs that include clinically important values.

Population 2: non-small cell lung cancer patients with non-squamous disease

Current treatment pathways in the UK show that patients with non-squamous locally advanced or metastatic NSCLC can receive any of the four PLAT-based third-generation chemotherapies (GEM, VNB, PAX or DOC) as a first-line treatment. At the time of the initial guideline recommendations,[18] the clinical effectiveness of these chemotherapy regimens for non-squamous histology was unknown as clinical effectiveness data were not assessed according to histology. In addition, patients with non-squamous disease can receive PEM + CIS. Despite recommendations for use of these treatments, no comprehensive

trial has directly compared all of these treatments in this patient population. Moreover, there are currently only two trials that have direct evidence comparing PEM + CIS[61] or PEM + CARB[62] with any of the four PLAT-based combinations (i.e. GEM + CIS[61] and GEM + CARB[62]). In this section, comparisons are attempted between the five drugs currently available to patients with non-squamous disease. It is assumed that the treatment effect for all PLAT-based third-generation chemotherapies is not dependent on histology as in the current NICE guideline.[7] The same data points for PLAT-based third-generation chemotherapies that were used for NSCLC patients with squamous disease ($n = 18$) with the addition of subgroup data from two PEM + PLAT trials were employed.[61,62] Analysis of TTP alone was not performed since none of the PEM studies presented data on TTP.

Table 24 presents a network of trials showing direct evidence on at least one of the outcomes of interest for all chemotherapy trials in the population with non-squamous disease.

Overall survival

The data points included in the direct meta-analysis and mixed-treatment comparison analyses for OS are described in the previous section on squamous population analyses (see *Overall survival*) in *Table 15* and the 15 pair-wise comparisons are summarised in the network diagram (see *Figure 5*). Analyses for OS were based on all 20 trials, involving 9553 randomly assigned patients and 7608 deaths. OS data used in the meta-analyses and mixed-treatment comparisons for the analyses in the non-squamous disease population were derived from the same 18 trials as the data used in the analyses in the squamous disease population, except for PEM, in which case the data used reflect its licensed population (patients with adenocarcinoma and large cell). *Table 25* presents a network of trials showing direct OS evidence for all chemotherapy trials in the population with non-squamous disease. *Figure 17* presents a network of trials with OS data used in the mixed-treatment comparison and meta-analysis in the population with non-squamous disease. Result summaries for all pair-wise comparisons between interventions from the direct meta-analysis and the mixed-treatment comparison analyses are presented in *Table 26*. Individual trial results and overall pooled results from both analyses are displayed as forest plots for each pair-wise comparison where possible. Results from the mixed-treatment comparison sensitivity analyses for OS are shown in *Appendix 18*.

Results of direct meta-analysis and mixed-treatment comparison for OS in trials in the population with non-squamous disease are shown in *Table 26*. GEM + PLAT compared with VNB + PLAT had the greatest number of head-to-head trials (eight trials[43,45,49,50,54,55,57,58]). There was no direct head-to-head trial in population with non-squamous disease for three comparisons; thus, relative treatment effects for these three comparisons are derived entirely from the indirect estimates of the mixed-treatment comparison analysis.

TABLE 24 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on at least one of the outcomes of interest in the population with non-squamous disease

Trials	GEM + CIS	VNB+CIS	PAX + CIS	DOC + CIS	PEM + CIS	GEM + CARB	VNB+CARB	PAX + CARB	DOC + CARB	PEM + CARB
Kelly 2001[48]		✗						✗		
Schiller 2002[47]	✗		✗	✗				✗		
Scagliotti 2002[43]	✗	✗						✗		
Fossella 2003[44]		✗		✗					✗	
Gebbia 2003[49]	✗	✗								
Gridelli 2003[45]	✗	✗								
Smit 2003[46]	✗		✗							
Chen 2004[51]		✗	✗							
Douillard 2005[53]		✗		✗						
Martoni 2005[54]	✗	✗								
Chen 2007[52]		✗		✗						
Helbekkmo 2007[55]						✗	✗			
Langer 2007[56]	✗							✗		
Ohe 2007[57]	✗	✗						✗		
Thomas 2006[58]		✗				✗				
Chang 2008[50]	✗	✗								
Scagliotti 2008[61]	✗				✗					
Gronberg 2009[62]						✗				✗
Tan 2009[59]		✗		✗						
Treat 2010[60]						✗		✗		
Total trials	**10**	**13**	**3**	**5**	**1**	**4**	**1**	**6**	**1**	**1**

TABLE 25 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on OS in the population with non-squamous disease

Trials	Data source for HR and variance	GEM + PLAT	VNB + PLAT	PAX + PLAT	DOC + PLAT	PEM + PLAT
Schiller 2002[47]	Le Chevalier 2005[79]	✗		✗	✗	
Kelly 2001[48]	Estimated HR from reported survival estimates using common approaches[66,67]		✗	✗		
Scagliotti 2002[43]	Published trial	✗	✗	✗		
Fossella 2003[44]	Published trial		✗		✗	
Gebbia 2003[49]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗			
Gridelli 2003[45]	Le Chevalier 2005[79]	✗	✗			
Smit 2003[46]	Le Chevalier 2005[79]	✗		✗		
Chen 2004[51]	Author through e-mail		✗	✗		
Douillard 2005[53]	Author through e-mail		✗		✗	
Martoni 2005[54]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗			
Chen 2007[52]	Author through e-mail		✗		✗	
Helbekkmo 2007[55]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗			
Langer 2007[56]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗		
Ohe 2007[57]	Published trial	✗	✗	✗		
Thomas 2006[58]	Author through e-mail	✗	✗			
Chang 2008[50]	Le Chevalier 2005[79]	✗	✗			
Scagliotti 2008[61]	Published trial	✗				✗
Gronberg 2009[62]	Author through e-mail	✗				✗
Tan 2009[59]	Estimated HR from reported survival estimates using common approaches[66,67]		✗		✗	
Treat 2010[60]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗		
Total trials		**14**	**14**	**8**	**5**	**2**

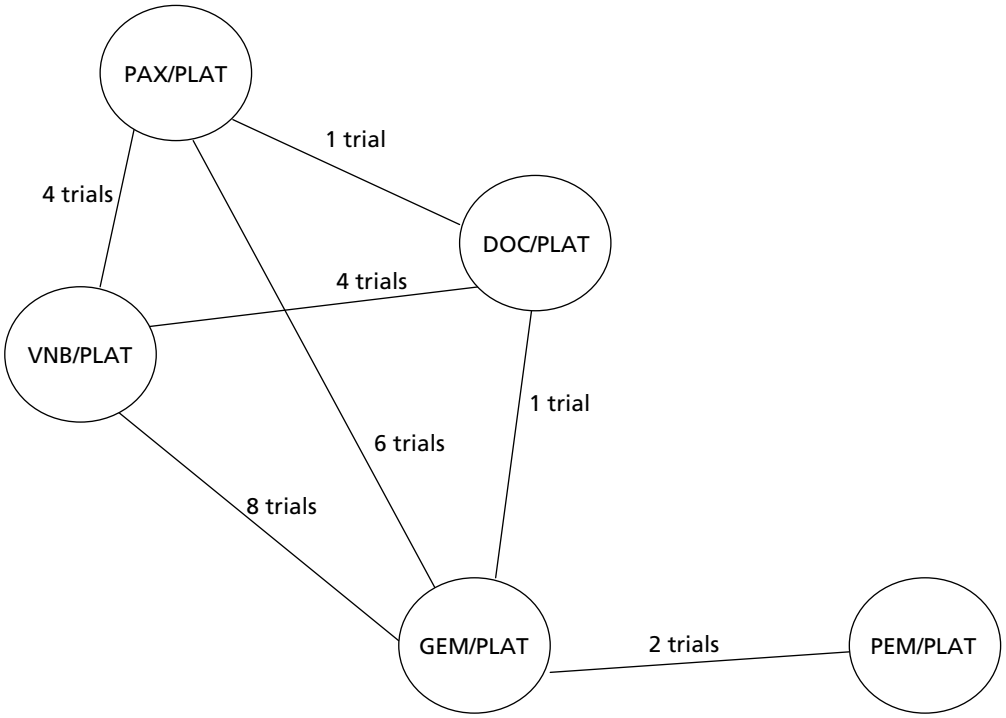

FIGURE 17 Network of RCTs comparing chemotherapy in the treatment of first-line advanced NSCLC (OS) for the mixed-treatment comparison and meta-analysis in the population with non-squamous disease.

TABLE 26 Results of direct meta-analysis and mixed-treatment comparison for OS in trials in the population with non-squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of events (deaths) in reference treatment/ comparator	Direct meta-analysis 1 ($n = 20$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 20$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57,58]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.08 (0.99 to 1.18)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.06 (0.97 to 1.16)
GEM + PLAT vs DOC + PLAT[47]	1	301/304	262/271	1.06 (0.89 to 1.28)	0.99 (0.87 to 1.13)
GEM + PLAT vs PEM + PLAT[61,62]	2	1084/1087	755/772	0.85 (0.73 to 1.00)	**0.85 (0.74 to 0.98)**
VNB + PLAT vs PAX + PLAT[43,48,51,57]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.92 (0.68 to 1.24)
VNB + PLAT vs DOC + PLAT[44,52,53,59]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.98 (0.87 to 1.09)
VNB + PLAT vs PEM + PLAT	0	XX	XX	XX	0.92 (0.82, 1.03)
PAX + PLAT vs DOC + PLAT[47]	1	602/304	538/271	0.98 (0.76 to 1.27)	**0.79 (0.66 to 0.93)**
PAX + PLAT vs PEM + PLAT	0	XX	XX	XX	0.85 (0.63 to 1.16)
DOC + PLAT vs PEM + PLAT	0	XX	XX	XX	0.94 (0.81 to 1.09)

XX, no direct meta-analysis evidence.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Bold text indicates statistically significant result.

Effect of other PLAT-based third-generation chemotherapies in the population with non-squamous disease (overall survival)

Results from the meta-analysis 1 and mixed-treatment comparison 1 analyses for these pair-wise comparisons (GEM + PLAT vs VNB + PLAT; GEM + PLAT vs PAX + PLAT; GEM + PLAT vs DOC + PLAT; VNB + PLAT vs PAX + PLAT; VNB + PLAT vs DOC + PLAT; and PAX + PLAT vs DOC + PLAT) in the population with non-squamous disease are shown in *Table 26*. With one exception, these results were identical to the meta-analysis 1 results from the analyses of NSCLC population with squamous disease and similar to the mixed-treatment comparison 1 results from the analyses of NSCLC population with squamous disease (see *Overall survival*). The exception was PAX + PLAT compared with DOC + PLAT. The mixed-treatment comparison 1 analysis shows a statistically significant difference between PAX + PLAT and DOC + PLAT (HR = 0.79; 95% CI 0.66 to 0.93); although the results of the direct meta-analysis 1 were not significant. There is insufficient evidence to conclude whether or not there is any difference between PAX + PLAT and DOC + PLAT in terms of OS in the population with non-squamous disease.

Gemcitabine plus platinum compared with pemetrexed plus platinum

Two head-to-head RCTs[61,62] with 2171 patients were eligible for comparison between GEM and PEM in combination with PLAT in the analysis of the population with non-squamous disease. The two PEM trials[61,62] used different PLAT-based regimens, with one trial[61] comparing PEM + CIS with GEM + CIS, and the other trial[62] comparing PEM + CARB with GEM + CARB.

The HR and 95% CI for each trial are displayed in *Figure 18* together with the pooled results from direct meta-analysis 1 and mixed-treatment comparison analyses. Visual examination of *Figure 18*, the chi-squared test for heterogeneity ($p = 0.253$) and the I^2-statistic (23.4%) all suggest good consistency; the test for heterogeneity is non-significant and the I^2-statistic is well below our pre-defined 50% cut-off point for moderate heterogeneity. The pooled OS estimate from meta-analysis 1 (HR = 0.85; 95% CI 0.73 to 1.00)

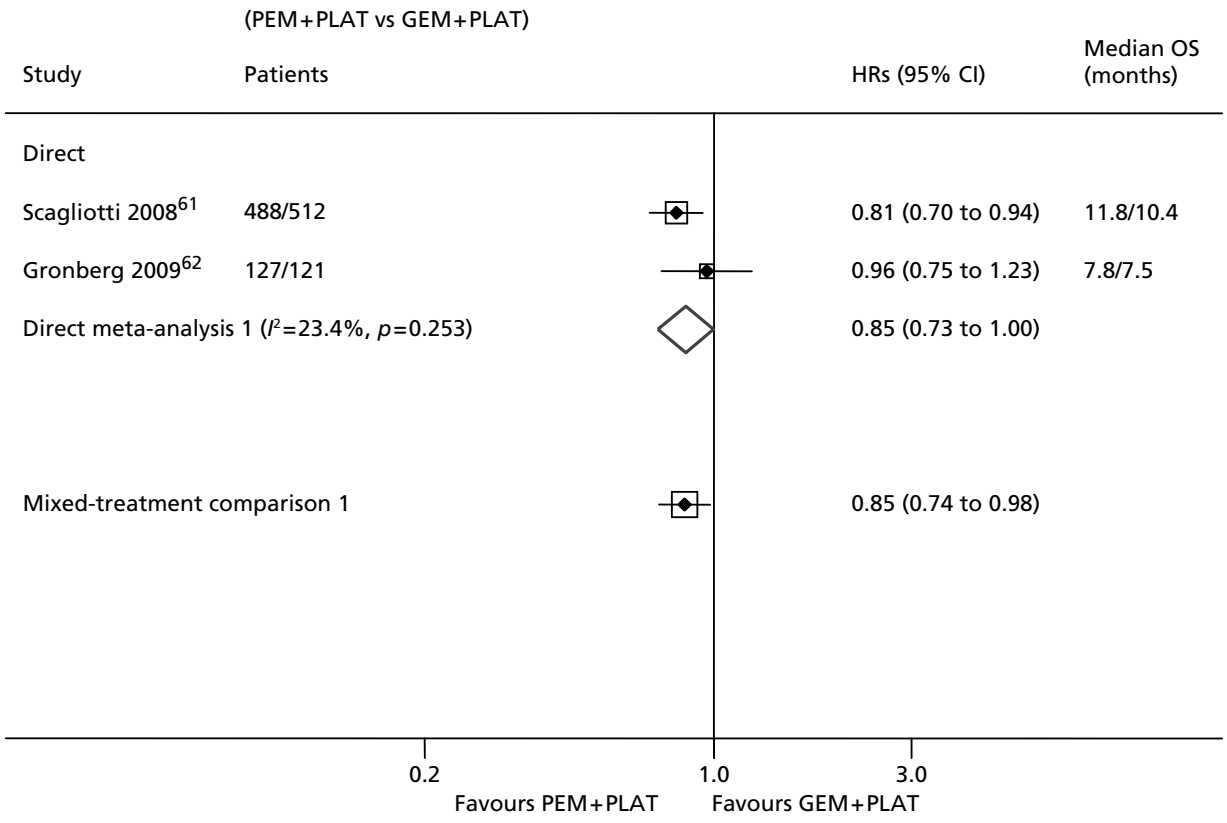

FIGURE 18 Forest plot illustrating results of direct meta-analysis and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing GEM + PLAT vs PEM + PLAT in the population with non-squamous disease.

was borderline statistically significant. The mixed-treatment comparison 1 result was statistically significant (HR = 0.85; 95% CI 0.74 to 0.98). These results suggest that there is evidence to support a difference in an OS benefit PEM + PLAT compared with GEM + PLAT. Median OS estimates were quite different across the two trials: in the Scagliotti *et al*. trial[61] median OS was 11.8 compared with 10.4 months and in the Gronberg *et al*. trial[62] median OS was 7.8 compared with 7.5 months for GEM + PLAT compared with PEM + PLAT, respectively. This difference could be because the proportion of patients who received postprogression treatment in the Scagliotti *et al*. trial[61] was much higher than in the Gronberg *et al*. trial[62] (54% and 32%, respectively). Alternatively, it could also be owing to other differences between the trials that we have not been able to explore.

Vinorelbine plus platinum compared with pemetrexed plus platinum

There was no trial that directly compared VNB + PLAT with PEM + PLAT in the population with non-squamous disease. Therefore, the OS comparison between these two treatment combinations was based entirely on results from the mixed-treatment comparison 1 analysis which suggest a non-significant improvement in OS on PEM + PLAT (HR = 0.92; 95% CI 0.82 to 1.03).

Paclitaxel plus platinum compared with pemetrexed plus platinum

There was no trial that directly compared PAX + PLAT and PEM + PLAT in the population with non-squamous disease. Therefore, the OS comparison between these two treatment combinations was based entirely on results from the mixed-treatment comparison 1 analysis which shows a non-statistically significant difference between PAX + PLAT and PEM + PLAT (HR = 0.85; 95% CI 0.63 to 1.16). There is insufficient evidence to conclude whether or not there is any difference between PEM + PLAT and PAX + PLAT in terms of OS in the population with non-squamous disease.

Docetaxel plus platinum compared with pemetrexed plus platinum

There was no trial that directly compared DOC + PLAT with PEM + PLAT in the population with non-squamous disease. Therefore, the comparisons of OS between these two treatments combinations were entirely based on results from the mixed-treatment comparison 1 analysis, which found a non-statistically significant difference between DOC + PLAT and PEM + PLAT (HR = 0.94; 95% CI 0.81 to 1.09). There is insufficient evidence to conclude whether or not there is any difference between DOC + PLAT and PEM + PLAT in the population with non-squamous disease.

Progression-free survival

The same data points used in the PFS analysis for the NSCLC population with squamous disease were used in this analysis except that the non-squamous specific PFS estimates for PEM + PLAT compared with GEM + PLAT from the two PEM trials were used.[61,62] *Table 27* shows pair-wise comparison results between GEM + PLAT, VNB + PLAT, PAX + PLAT, DOC + PLAT and PEM + PLAT from the direct meta-analyses and the mixed-treatment comparison analyses. Eight trials[45,47,51–54,56,61] were included in the PFS analysis detailed in *Table 28*. Results from the mixed-treatment comparison sensitivity analyses for OS are shown in *Appendix 19*. *Appendices 20* and *21* shows results for direct meta-analysis and mixed-treatment comparison for combined PFS/TTP analyses.

The data points included in the direct meta-analyses and mixed-treatment comparison analyses for PFS are presented in *Table 18* and 10 pair-wise comparisons are summarised in *Figure 19*. Analysis of PFS was based on eight trials involving 4396 patients. The HRs for PFS from one trial[61] were extracted from the trial papers and data from three trials[51–53] were obtained by contacting the investigators. Data from two trials[45,47] were extracted from a systematic review,[79] as HRs were not reported in the primary trial publication (as noted earlier, three out of four investigators in the primary trials were also co-authors for this systematic review). The remaining two trials did not report HRs for PFS[54,56] and so the HRs and associated variance were extracted using information on PFS outcome by applying pre-specified methods[66,67] as described in *Evidence synthesis.*

A network of eight connected RCTs[45,47,51–54,56,61] with 10 different treatment comparisons are presented in *Table 29* and *Figure 19*. The circles in *Figure 19* represent different treatments, and the lines represent

TABLE 27 Summary results of direct meta-analysis and mixed-treatment comparison of PFS in trials in the population with non-squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of PFS events in reference treatment/ comparator	Direct meta-analysis 1 ($n = 8$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 8$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[45,54]	2	269/269	312[a]	1.09 (0.87 to 1.38)	1.06 (0.78 to 1.66)
GEM + PLAT vs PAX + PLAT[47,56]	2	350/651	142/304[b]	1.17 (1.00 to 1.36)	1.23 (0.77 to 1.65)
GEM + PLAT vs DOC + PLAT[47]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.7 to 1.61)
GEM + PLAT vs PEM + PLAT[61]	1	1084/1087	NR	0.90 (0.79 to 1.02)	0.90 (0.53 to 1.52)
VNB + PLAT vs PAX + PLAT[51]	1	70/70	7/14[b]	**1.52 (1.06 to 2.17)**	1.16 (0.6 to 1.65)
VNB + PLAT vs DOC + PLAT[52,53]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.61 to 1.44)
VNB + PLAT vs PEM + PLAT	XX	XX	XX	XX	0.85 (0.42 to 1.51)
PAX + PLAT vs DOC + PLAT[47]	1	602/304	130/263[b]	0.97 (0.75 to 1.24)	0.88 (0.59 to 1.52)
PAX + PLAT vs PEM + PLAT	XX	XX	XX	XX	0.73 (0.42 to 1.53)
DOC + PLAT vs PEM + PLAT	XX	XX	XX	XX	0.83 (0.43 to 1.65)

XX, no direct meta-analysis evidence.

a Number of events are for both arms; XX=no direct meta-analysis evidence.

b Includes PD only as PFS event (PD or death) not reported.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Bold text indicates a statistically significant result.

TABLE 28 Definitions of PFS used in trials that were eligible for inclusion in the NSCLC population with non-squamous disease

Trial	Trial definitions of PFS
Schiller 2002[47]	TTP was calculated from the date of enrolment to the date of progression or death
Gridelli 2003[45]	TTP was defined as the interval from date of random assignment to treatment and date of progression or death
Chen 2004[51]	TTP was calculated from the date of initiation of treatment to the date of disease progression or death
Douillard 2005[53]	TTP was defined as the time from random assignment to the first evidence of progressive disease or death
Martoni 2005[54]	TTP was defined as the time from random assignment to the first evidence of progressive disease or death, if progression was not documented
Chen 2007[52]	TTP was calculated from the date of initiation of treatment to the date of disease progression or death
Langer 2007[56]	PFS was defined as time from random assignment to tumour progression or death without documented disease progression
Scagliotti 2008[61]	PFS: disease status was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST)

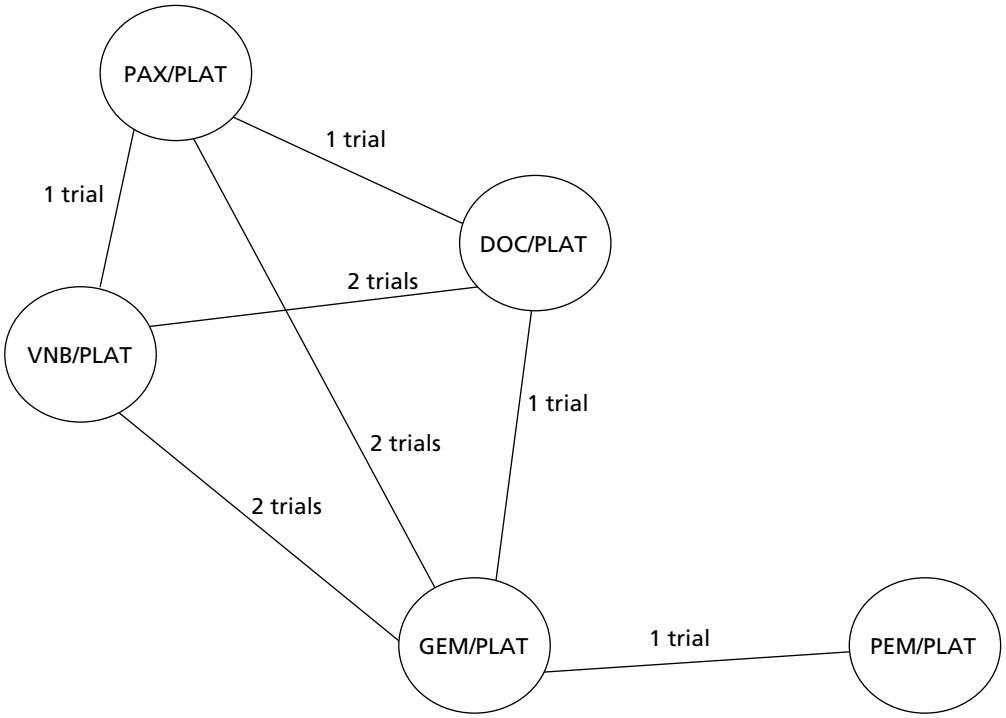

FIGURE 19 Network of RCTs comparing chemotherapy in the treatment of first-line advanced NSCLC PFS for the meta-analysis and mixed-treatment comparison analyses of the population with non-squamous disease.

TABLE 29 Network of trials showing direct evidence for eight chemotherapy trials with ✗ reflecting available data on PFS in the population with non-squamous disease

Trials	Data source for HR and variance	GEM + PLAT	VNB + PLAT	PAX + PLAT	DOC + PLAT	PEM + PLAT
Schiller 2002[47]	Le Chevalier 2005[79]	✗		✗	✗	
Gridelli 2003[45]	Le Chevalier 2005[79]	✗	✗			
Chen 2004[51]	Author through e-mail		✗	✗		
Douillard 2005[53]	Author through e-mail		✗		✗	
Martoni 2005[54]	Estimated HR from reported survival estimates using common approaches[66,67]	✗	✗			
Chen 2007[52]	Author through e-mail		✗		✗	
Langer 2007[56]	Estimated HR from reported survival estimates using common approaches[66,67]	✗		✗		
Scagliotti 2008[61]	Published trial	✗				✗
Total trials		**5**	**5**	**3**	**3**	**1**

direct head-to-head trials informing each comparison. Unconnected circles indicate a lack of direct randomised comparison. There was no direct evidence for the following comparisons: VNB + PLAT compared with PEM + PLAT; PAX + PLAT compared with PEM + PLAT; and DOC + PLAT compared with

PEM + PLAT. Relative treatment effects for these comparisons are estimated entirely from the indirect evidence available from the mixed-treatment comparison analysis.

Effect of other PLAT-based third-generation chemotherapies in the population with non-squamous disease (progression-free survival)

Results from the meta-analysis 1 and mixed-treatment comparison 1 analyses for these pair-wise comparisons (GEM + PLAT vs VNB + PLAT; GEM + PLAT vs PAX + PLAT; GEM + PLAT vs DOC + PLAT; VNB + PLAT vs PAX + PLAT; VNB + PLAT vs DOC + PLAT; and PAX + PLAT vs DOC + PLAT) in the non-squamous population are shown in *Table 27*.

Gemcitabine plus platinum compared with pemetrexed plus platinum

A single trial[61] provided direct evidence for GEM + PLAT compared with PEM + PLAT, with 1725 patients contributing to this comparison. The PLAT-based regimen was the same in both arms; thus, this analysis can be considered as a comparison of GEM and PEM when in combination with CIS. The HR and 95% CI from this trial are presented in *Table 27* together with the pooled HR estimates from mixed-treatment comparison analyses. The direct PFS estimated from this trial suggests a potential benefit for PEM + PLAT, although the difference was not statistically significant (HR = 0.90; 95% CI 0.79 to 1.02). This result appears to be similar and consistent with the results from the mixed-treatment comparison 1 analysis, albeit with a much wider CI (HR = 0.90; 95% CI 0.53 to 1.52). These findings, therefore, indicate that there is insufficient evidence to conclude whether or not there are differences in PFS between GEM + PLAT and PEM + PLAT in the population with non-squamous disease.

Vinorelbine plus platinum compared with pemetrexed plus platinum

There was no trial that directly compared VNB + PLAT with PEM + PLAT. Therefore, the PFS comparison between these two drugs was based entirely on the results from the mixed-treatment comparison analyses. The results from the mixed-treatment comparison analyses were not statistically significant (HR = 0.85; 95% CI 0.42 to 1.51; mixed-treatment comparison 1). These findings indicate that there is insufficient evidence to conclude whether or not there are differences in PFS between VNB + PLAT and PEM + PLAT in population with non-squamous disease.

Paclitaxel plus platinum compared with pemetrexed plus platinum

There was no trial that directly compared PAX + PLAT with PEM + PLAT. Therefore, the PFS comparison between these two drugs was based entirely on results from the mixed-treatment comparison 1 analysis. The results from this analysis showed no significant difference in PFS between PAX + PLAT and PEM + PLAT (HR = 0.73; 95% CI 0.42 to 1.53; mixed-treatment comparison 1). These findings indicate that there is insufficient evidence to conclude whether or not there are differences in PFS between PAX + PLAT and PEM + PLAT in the population with non-squamous disease.

Docetaxel plus platinum compared with pemetrexed plus platinum

There was no head-to-head trial that compared DOC + PLAT with PEM + PLAT. Therefore, the PFS comparison between these two drugs was based entirely on results from the mixed-treatment comparison 1 analyses. The results from this analysis showed no significant difference in PFS between DOC + PLAT and PEM + PLAT (HR = 0.83; 95% CI 0.43 to 1.65; mixed-treatment comparison 1). These findings indicate that there is insufficient evidence to conclude whether or not there are differences in PFS between DOC + PLAT and PEM + PLAT in the population with non-squamous disease.

Survival risk at year 1 and year 2 post randomisation

Year 1 and year 2 survival risks were defined as the probability of survival in intervals of time elapsed from randomisation to years 1 and 2, respectively. The same data points used in the year 1 and year 2 analyses for the NSCLC population with squamous disease were used in this analysis except that the non-squamous specific estimates for PEM + PLAT compared with GEM + PLAT from the two PEM trials were used.[61,62] Results for meta-analysis and mixed-treatment comparison analyses for 1-year and 2-year survival

are shown in *Appendices 22* and *23*, respectively. None of the results from the 2-year analyses were statistically significant with wide CIs that include clinically important values.

Epidermal growth factor receptor mutation-positive population

Three RCTs[15,63–65] that compared GEF to PLAT-based chemotherapy as a first-line treatment of patients with advanced NSCLC were eligible for inclusion in the analysis of the EGFR M+ population. This is the first time that data from the Mitsudomi *et al*.[65] and Maemondo *et al*.[63] trials have been used in any meta-analysis or mixed-treatment comparison analyses within this report. All three trials[15,63–65] were conducted in patients from East Asian populations who were identified as having adenocarcinoma, and being never or light smokers. Patients were randomised to GEF arms or to chemotherapy. Those in chemotherapy arms received different PLAT-based combinations: PAX + CARB in two trials[15,63,64] and DOC + CIS in one trial.[65] Patient characteristics in the three trials[15,63–65] appear to be similar; however, the selection of patients differed across the three trials. In the IPASS[15,64] patient enrolment was not restricted to patients who were EGFR M+, whereas in the two trials[63,65] only EGFR M+ patients were randomised. Therefore, the EGFR M+ data used in this report from the IPASS[15,64] are restricted to the subgroup of patients classified as EGFR M+. OS and PFS were reported in all three trials; however, TTP and survival rates were not reported by EGFR M+ status.

Overall survival

Overall survival was defined consistently across the three trials[15,63–65] as time from randomisation to death from any cause. The data points included in the direct meta-analyses and mixed-treatment comparison analyses for OS are presented in *Table 30* and three pair-wise comparisons are summarised in *Figure 20*. Analysis for OS was based on the results of all three trials, involving 663 randomly assigned patients. HRs for OS for two trials[15,64,65] were extracted from the trial papers and OS data for one trial[63] were obtained by contacting the trial investigator. Three treatments (GEF, PAX + PLAT and DOC + PLAT) qualified for inclusion in the analysis of the EGFR M+ population. A network of connected RCTs with different treatment comparisons is presented in *Table 30* and *Figure 20*. The nodes in *Figure 20* represent different treatments, and the lines represent direct head-to-head trials informing each comparison. Unconnected nodes indicate lack of direct randomised comparison. There were two direct head-to-head comparisons PAX + PLAT compared with GEF[15,63,64] and DOC + PLAT compared with GEF.[65] There was no direct evidence for the PAX + PLAT compared with DOC + PLAT comparison.

Result summaries for all pair-wise comparisons between interventions from the direct meta-analyses and the mixed-treatment comparison analyses including individual trial results are presented in *Table 31*.

TABLE 30 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on OS in the EGFR M+ population

Trials	Data source for HR and variance	PAX + PLAT	DOC + PLAT	GEF
Mok 2009[15] and Fukuoka 2011[64]	Published trial	✗		✗
Maemondo 2010[63]	Author through e-mail	✗		✗
Mitsudomi 2010[65]	Published trial		✗	✗
Total trials		**2**	**1**	**3**
Total number of deaths		**95**[a]	**NR**	**104**[a]
Total number of patients		**242**	**86**	**246**

NR, not reported.

a Number of death events from Maemondo *et al*.[63] was not reported, so total number of deaths for PAX + PLAT and GEF could be higher than the figure shown in this table.

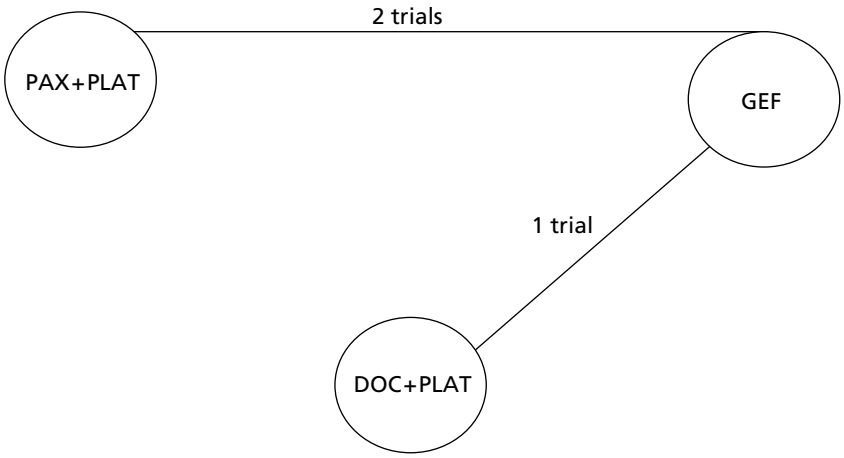

FIGURE 20 Network of RCTs comparing GEF and chemotherapy used in the meta-analysis and mixed-treatment comparison analyses in the EGFR M+ population.

TABLE 31 Results of direct meta-analysis and mixed-treatment comparison for OS in trials in the EGFR M+ population

Reference treatment vs comparator	Total deaths/patients in both arms	Direct meta-analysis ($n = 3$) HR (95% CI)	Mixed-treatment comparison ($n = 3$), HR (95% CI)
PAX + PLAT vs GEF[15,63,64]	199[a]/448	0.94 (0.74 to 1.18)	0.94 (0.67 to 1.3)
DOC + PLAT vs GEF[65]	NR/172	1.64 (0.75 to 3.58)[b]	1.64 (0.54 to 4.96)
PAX + PLAT vs DOC + PLAT	XX	XX	0.57 (0.18 to 1.81)

XX, no direct meta-analysis evidence; NR not reported.

a Not reported in one trial.[63]

b Direct evidence.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Paclitaxel plus platinum compared with gefitinib

Two head-to-head RCTs[15,63,64] including 484 patients were available that compared GEF and PAX + PLAT and contributed to the OS analysis in the EGFR M+ population. Both trials used CARB as the PLAT agent; thus, this analysis can be considered to compare PAX + CARB with GEF. The HR and 95% CI for each trial are displayed in *Table 31* and *Figure 21* together with the pooled meta-analysis result and HRs from the mixed-treatment comparison analyses. Visual examination of *Figure 21*, the non-significant chi-squared test for heterogeneity ($p = 0.394$) and the I^2-statistic (0%) all suggest very good consistency. The pooled direct HR (HR = 0.94; 95% CI 0.74 to 1.18; meta-analysis for PAX + PLAT vs GEF) shows no significant difference in OS between GEF and PAX + PLAT. The direct meta-analysis evidence is consistent with the results of the mixed-treatment comparison analyses.

Docetaxel plus platinum compared with gefitinib

One head-to-head RCT[65] including 172 patients was available that compared GEF with DOC + PLAT and contributed to the OS analysis in the EGFR M+ population. This trial used CARB as the PLAT agent. The HR and 95% CI for this trial are displayed in *Table 31* together with the pooled meta-analysis and HR results from the mixed-treatment comparison analyses. The direct HR (HR = 1.64; 95% CI 0.75 to 3.58) suggests a lack of evidence of any difference in OS between GEF and DOC + PLAT. The direct evidence is consistent with the results of the mixed-treatment comparison analyses in terms of HR and 95% CI (i.e. not statistically significant). The wide CI is a reflection of few deaths from immature OS data (only 10 deaths at data cut-off).

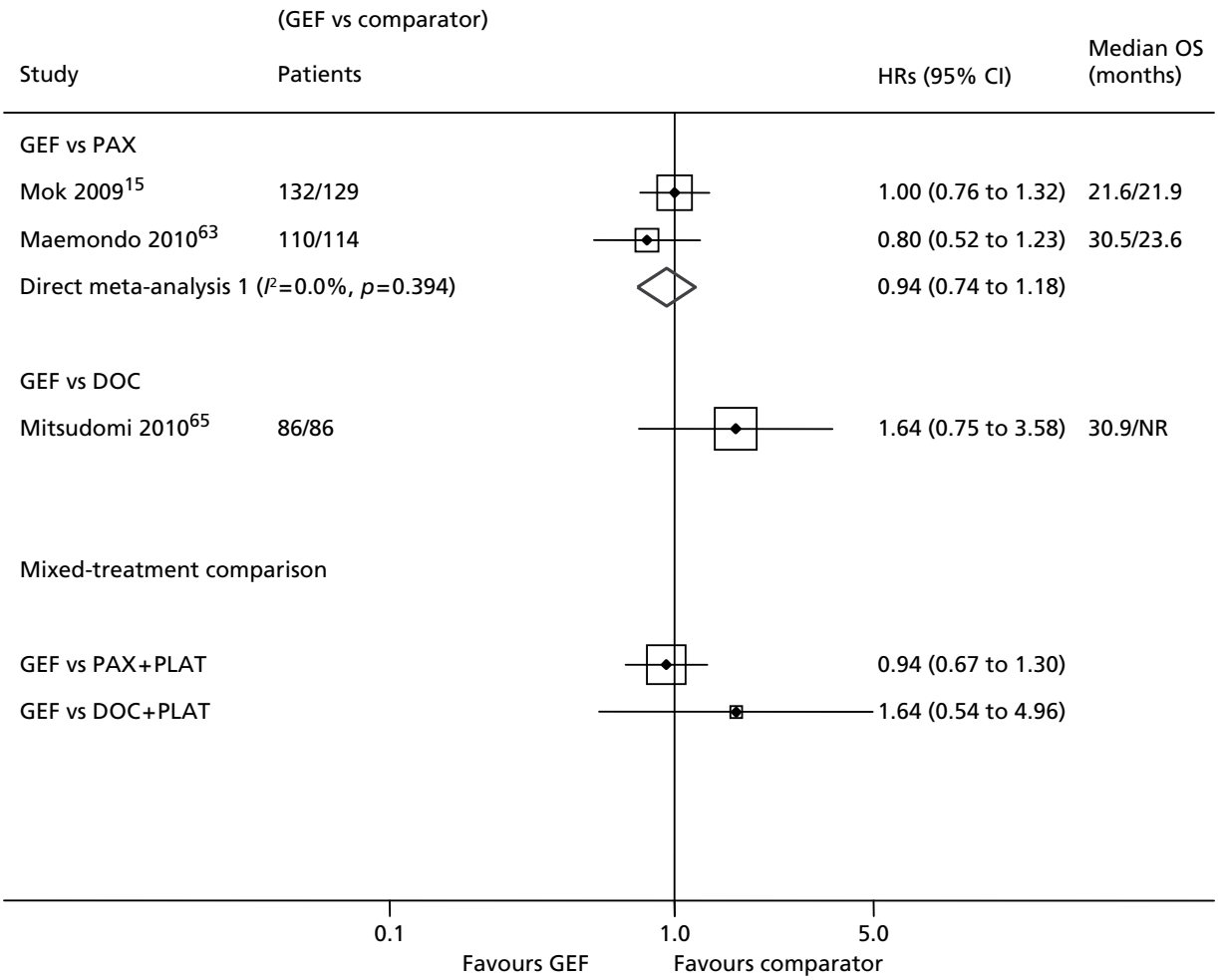

FIGURE 21 Forest plot illustrating results of direct meta-analysis and mixed-treatment comparison in terms of HRs and 95% CI of OS in trials comparing GEF vs PAX + PLAT and GEF vs DOC + PLAT in the EGFR M+ population.

Paclitaxel plus platinum compared with docetaxel plus platinum

There was no trial that directly compared PAX + PLAT with DOC + PLAT in the EGFR M+ population. Therefore, OS comparison between these two drugs was estimated from the mixed-treatment comparison analysis that included three trials.[15,63–65] The results from the mixed-treatment comparison analysis showed no significant difference in OS between PAX + PLAT and DOC + PLAT (HR = 0.57; 95% CI 0.18 to 1.81). These findings indicate that there is insufficient evidence to conclude whether or not there are differences in OS between PAX + PLAT and DOC + PLAT in EGFR M+ patients; indeed, the wide CIs associated with the HR may point to clinically important differences in both directions.

Progression-free survival

The definition of PFS was consistent across the three trials[15,63–65] and all trials adopted Response Evaluation Criteria in Solid Tumours (RECIST)[81] to assess tumour progression. The HRs for PFS were available from all trials. The data points included in the direct meta-analyses and mixed-treatment comparison analyses for PFS are presented in *Table 32* and three pair-wise comparisons are summarised in *Figure 22*. Analysis for PFS was based on outcome data for 660 randomly assigned patients. Three treatments (GEF, PAX + PLAT and DOC + PLAT) qualified for inclusion in the analysis in the EGFR M+ population. A network of connected RCTs with different treatment comparisons is presented in *Table 32* and *Figure 22*. The nodes represent different treatments, and the lines represent direct head-to-head trials informing each comparison. Unconnected nodes indicate lack of direct randomised comparison. There were two direct

TABLE 32 Network of trials showing direct evidence for all chemotherapy trials with ✗ reflecting available data on PFS in the EGFR M+ population

Trials	Data source for HR and variance	PAX + PLAT	DOC + PLAT	GEF
Mok 2009[15] and Fukuoka 2011[64]	Published trial	✗		✗
Maemondo 2010[63]	Published trial	✗		✗
Mitsudomi 2010[65]	Published trial		✗	✗
Total trials		**2**	**1**	**3**
Total number of PFS events		Not reported in all trials[63,65]	Not reported in all trials[63,65]	Not reported in all trials[63,65]
Total number of patients		**242**	**86**	**332**

Number of PFS events from Maemondo *et al.*[63] and Mitsudomi *et al.*[65] were not reported, so total number of deaths for PAX + PLAT and GEF could be higher than what is shown in this table.

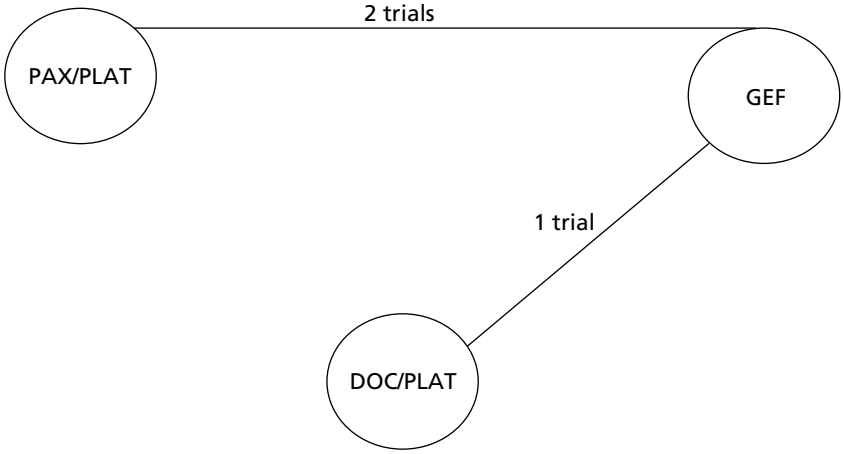

FIGURE 22 Network of RCTs comparing GEF and chemotherapy used in the PFS meta-analysis and mixed-treatment comparison analyses in the EGFR M+ population.

head-to-head comparisons (PAX + PLAT vs GEF and DOC + PLAT vs GEF). There was no direct evidence for PAX + PLAT compare with DOC + PLAT.

Result summaries for all pair-wise comparisons between interventions from the direct meta-analyses and the mixed-treatment comparison analyses including individual trials results are presented in *Table 33* and *Figure 23*.

Paclitaxel plus platinum compared with gefitinib

Two head-to-head RCTs[15,63,64] including 491 patients were available that compared GEF and PAX + PLAT and contributed to the PFS analysis in the EGFR M+ population. Both trials used CARB as the PLAT. The HR and 95% CI for each trial are displayed in *Table 33* together with the pooled meta-analysis results and HRs from mixed-treatment comparison analyses. Visual examination of *Figure 23*, a statistically significant chi-squared test for heterogeneity ($p = 0.03$) and the I^2-statistic (78.8%) all suggested inconsistency in the direct evidence from the two trials[15,63,64] comparing PAX + PLAT and GEF. However, both trials showed that GEF is significantly better than PAX + PLAT in terms of improving PFS in patients with the EGFR M+ population. The pooled direct meta-analysis HR (HR = 0.38; 95% CI 0.24 to 0.60) suggests evidence of a significant difference in PFS between GEF and PAX + PLAT. The direct evidence is consistent with the results

TABLE 33 Results of direct meta-analysis and mixed-treatment comparison for PFS in trials in the EGFR M+ population

Reference treatment vs comparator	Total PFS events/ patients in both arms	Direct meta-analysis ($n = 3$), HR (95% CI)	Mixed-treatment comparison ($n = 3$), HR (95% CI)
PAX + PLAT vs GEF[15,63,64]	NR/488	**0.38 (0.24 to 0.60)**	**0.39 (0.29 to 0.52)**
DOC + PLAT vs GEF[65]	NR/172	**0.49 (0.33 to 0.73)**[a]	**0.49 (0.28 to 0.86)**
PAX + PLAT vs DOC + PLAT	XX	XX	0.79 (0.42 to 1.48)

XX, no direct meta-analysis evidence.
a Direct evidence.
A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.
Bold text indicates statistically significant result.

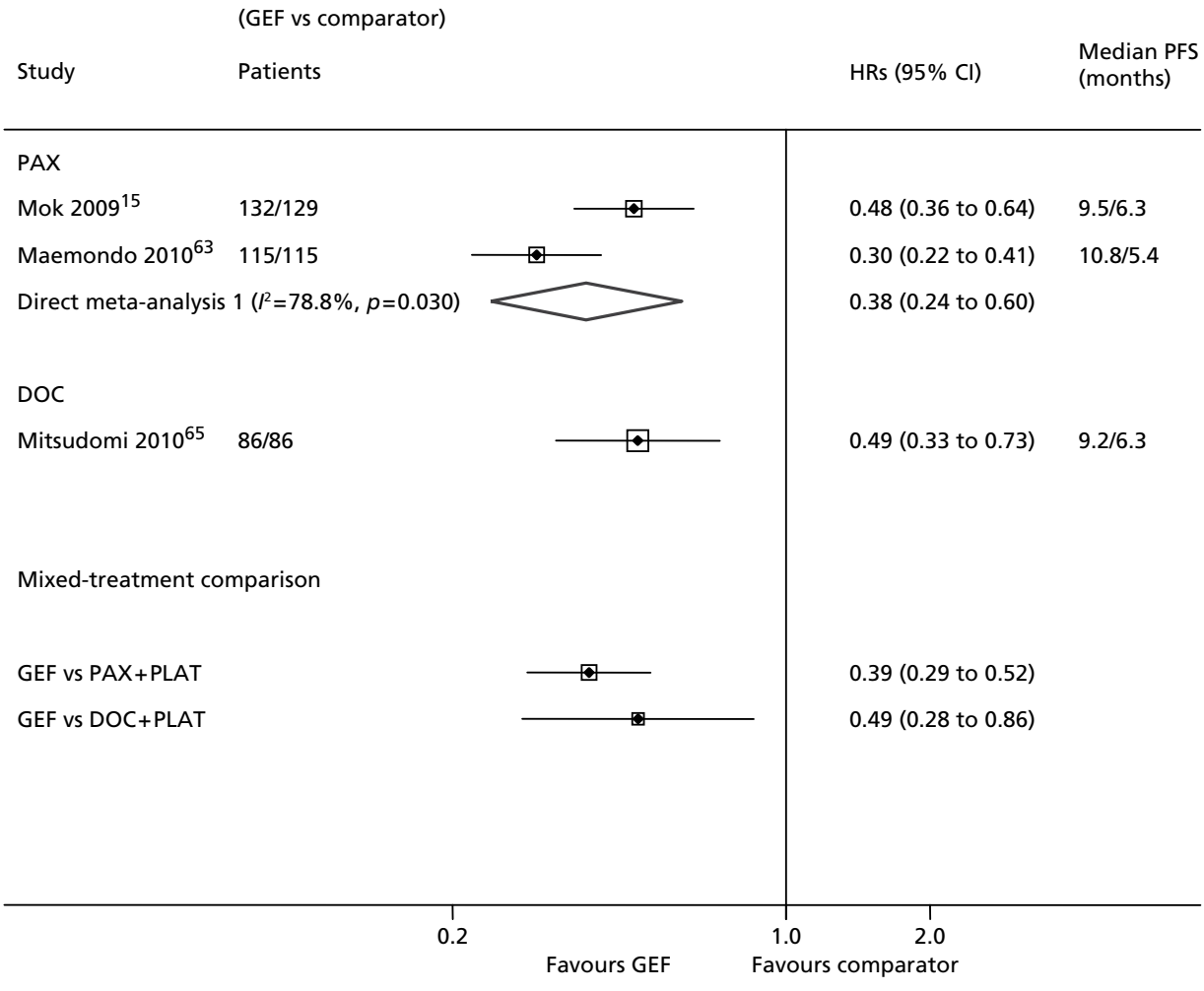

FIGURE 23 Forest plot illustrating results of direct meta-analyses and mixed-treatment comparisons in terms of HRs and 95% CI of PFS in trials comparing GEF vs PAX + PLAT and GEF vs DOC + PLAT in the EGFR M+ population.

of the mixed-treatment comparison analysis in terms of HR and 95% CI (i.e. statistically significant). Further investigation is required to explore the heterogeneity between trials. Given the significant evidence of heterogeneity, which is above a pre-specified 50% (moderate heterogeneity[68,69]) in the direct meta-analysis between PAX + PLAT and GEF, the pooled PFS HR should be interpreted with a degree of caution.

Docetaxel plus platinum compared with gefitinib

One head-to-head RCT[65] including 172 patients was available that compared GEF with DOC + PLAT and contributed to the PFS analysis in the EGFR M+ population. This trial used CARB as the PLAT. The HR and 95% CI for this trial are displayed in *Table 33* together with the pooled result and HRs from mixed-treatment comparison analyses. The direct PFS HR (HR = 0.49; 95% CI 0.33 to 0.73) suggests evidence of a significant difference in PFS between GEF and DOC + PLAT. The direct evidence is consistent with mixed-treatment comparison analysis in terms of HR and 95% CI (i.e. statistically significant in favour of GEF). In addition, median PFS were 6.3 and 9.2 months in the DOC + PLAT and GEF arms, respectively.

Paclitaxel plus platinum compared with docetaxel plus platinum

There was no trial that directly compared PAX + PLAT with DOC + PLAT in the EGFR M+ population. Therefore, the PFS comparison between these two chemotherapy treatments was estimated from the mixed-treatment comparison analysis that included three trials.[15,63,65] The findings indicate that there is insufficient evidence to conclude whether or not there are differences in PFS between PAX + PLAT and DOC + PLAT; the wide CIs associated with the HR may point to clinically important differences in both directions (HR = 0.79; 95% CI 0.42 to 1.48).

Adverse events

This review presents data on AEs that were categorised in the published trials as being grade 3 and 4. *Appendix 24–26* provides details of the proportion of patients who experience grade 3–4 AEs within each individual trial and toxic deaths reported within each trial.

The trials reported a diverse range of AEs and the definitions of AEs (including grading) varied between trials, making it difficult to summarise AE data. *Tables 34–37* show statistically significant AEs reported within the trials by pair-wise group comparisons.

TABLE 34 Statistically significant grade 3–4 AEs – GEM + PLAT vs VNB + PLAT

Grade 3–4 AEs	GEM + PLAT	VNB + PLAT
Haematological toxicity		
Anaemia	Helbekkmo 2007[55]	
Leucopenia		Helbekkmo 2007[55]
Neutropenia		Chang 2008[50] Martoni 2005[54] Scagliotti 2002[43] Thomas 2006[58]
Platelets	Gebbia 2003[49]	
Thrombocytopenia	Chang 2008[50] Helbekkmo 2007[55] Martoni 2005[54] Scagliotti 2002[43] Thomas 2006[58]	
Non-haematological toxicity		
Asthenia	Gebbia 2003[49]	
Phlebitis		Gebbia 2003[49]
Vomiting		Chang 2008[50] Scagliotti 2002[43]

Table 34 shows that five trials[43,50,54,55,58] report significantly higher levels of thrombocytopenia in GEM + PLAT arms compared with VNB + PLAT arms. However, four trials[43,50,54,58] report significantly greater levels of neutropenia in VNB + PLAT arms compared with GEM + PLAT arms.

Table 35 indicates that haematological toxicity is more common in patients receiving GEM + PLAT (anaemia, blood transfusions, haemorrhage and thrombocytopenia) compared with patients receiving PAX + PLAT.

Table 36 indicates that haematological toxicity is more common in patients treated with VNB + PLAT compared with patients treated with PAX + PLAT.

Table 37 shows that anaemia and febrile neutropenia were significantly more common in patients treated with VNB + PLAT compared with patients treated with DOC + PLAT. Diarrhoea and alopecia are more common in patients treated with DOC + PLAT compared with patients treated with VNB + PLAT.

TABLE 35 Statistically significant grade 3–4 AEs – GEM + PLAT vs PAX + PLAT

Grade 3–4	GEM + PLAT	PAX + PLAT
Haematological toxicity		
Anaemia	Schiller 2002[47] Smit 2003[46] Treat 2010[60]	
Red blood cell transfusion	Scagliotti 2002[43] Smit 2003[46]	
Platelet transfusion	Scagliotti 2002[43] Treat 2010[60]	
Febrile neutropenia		Schiller 2002[47]
Haemorrhage	Smit 2003[46] Treat 2010[60]	
Neutropenia	Treat 2010[60]	Langer 2007[56]
Platelet count	Schiller 2002[47]	
Thrombocytopenia	Langer 2007[56] Scagliotti 2002[43] Smit 2003[46] Treat 2010[60]	
Non-haematological toxicity		
Alopecia		
Arthralgia		Treat 2010[60]
Myelosuppression	Smit 2003[46]	
Nausea/vomiting	Langer 2007[56]	
Renal toxic effects	Schiller 2002[47]	
Sensory neuropathy		Langer 2007[56] Treat 2010[60]
Fatigue	Langer 2007[56]	

TABLE 36 Statistically significant grade 3–4 AEs – VNB + PLAT vs PAX + PLAT

Grade 3–4	VNB + PLAT	PAX + PLAT
Haematological toxicity		
Anaemia	Scagliotti 2002[43]	
Blood transfusions	Scagliotti 2002[43]	
Leucopenia	Chen 2004[51] Kelly 2001[48]	
Neutropenia	Chen 2004[51] Kelly 2001[48] Scagliotti 2002[43]	
Thrombocytopenia		Scagliotti 2002[43]
Non-haematological toxicity		
Constipation		
Myalgia	Scagliotti 2002[43]	Chen 2004[51]
Myelosuppression	Chen 2004[51]	
Nausea/vomiting	Kelly 2001[48] Scagliotti 2002[43]	
Peripheral neuropathy		Chen 2004[51] Kelly 2001[48]

TABLE 37 Statistically significant grade 3–4 AEs – VNB + PLAT vs DOC + PLAT

Grade 3–4	VNB + PLAT	DOC + PLAT
Haematological toxicity		
Anaemia	Douillard 2005[53] Fossella 2003[44] Tan 2009[59]	
Febrile neutropenia	Douillard 2005[53] Tan 2009[59]	
Neutropenia	Douillard 2005[53]	Tan 2009[59]
Non-haematological toxicity		
Alopecia		Chen 2007[52] Douillard 2005[53]
Diarrhoea		Chen 2007[52] Fossella 2003[44]
Infection	Douillard 2005[53]	
Nail disorder		Douillard 2005[53]
Nausea/vomiting	Fossella 2003[44]	Douillard 2005[53]

Other data relating to AEs, including details of treatment administration and relative dose intensity (RDI), are presented in *Appendix 27*. Trials reported details of median time to complete treatment, percentage of patients who completed treatment as per protocol, details of chemotherapy dose reductions and delays, and median number of chemotherapy cycles.

The number of patients discontinued who treatment because of toxicity was significantly higher in the VNB + CIS treatment arm than in the PAX + CARB or DOC + CIS arms. In the trial by Kelly *et al.*,[48] discontinuation was significantly higher, and completion of treatment and RDI significantly lower, in the VNB + CIS arm than in the PAX + CARB arm. In the trial by Fossella *et al.*,[44] patients in the DOC + CIS and the DOC + CARB arms had a higher median number of chemotherapy cycles, higher RDI and completion rates and fewer treatment delays than those in the VNB + CIS arm. Patients in the DOC + CIS arm of the trial by Douillard *et al.*[53] had a higher median RDI, fewer cycle delays and fewer chemotherapy dose reductions compared with the VNB + CIS arm.

There was higher RDI for GEM compared with VNB in the trial by Thomas *et al.*[58] However, in a trial by Helbekkmo *et al.*,[55] a significantly greater percentage of patients in the GEM arm had >24 days between chemotherapy courses and delayed or cancelled chemotherapy at day 8 due to haematological toxicity compared with the VNB arm.

In the trial by Scagliotti *et al.*,[61] dose adjustments were less frequent and RDI was higher in the PEM arm than in the GEM arm. In the trial by Gronberg *et al.*,[62] the mean number of cycles was higher and significantly more patients in the PEM arm than in the GEM arm completed four cycles, and without delays.

In the trial by Schiller *et al.*,[47] treatment with GEM + CIS was more likely to cause grade 3, 4 or 5 renal toxicity and 27% of patients who received GEM + CIS were withdrawn from the trial owing to complications of therapy, compared with 15% of patients in the PAX + CIS arm ($p < 0.001$).

Gefitinib is associated with significantly lower severe toxic AEs compared with PAX + CARB[15,63,64] and DOC + CIS[65] with the exception of liver dysfunction.[65] In one trial, GEF[15,64] was associated with a lower rate of AEs leading to discontinuation of the drug (6.9% vs 13.6%) and a lower rate of dose modification due to toxic effects (16.1% vs 35.2% for CARB and 37.5% for PAX). AEs leading to death occurred in 3.8% of the patients treated with GEF and in 2.7% of the patients treated with PAX + CARB. Interstitial lung disease was significantly more common in patients treated with GEF than in those treated with PAX + CARB or DOC + CIS, including one fatality in each trial.[15,63–65]

Table 38 shows the top 10 AEs that occur in the greatest proportion of patients across all arms that use each chemotherapy. The AEs are all grades 3 and 4 (with the exception of one trial[58] in *Table 38* in which the grades for febrile neutropenia were not specified for either arm); however, reporting of AEs varied (for example grade 3 only, grade 4 only, grade 3 or grade 4 and grade 3 plus grade 4). Certain AEs were grouped together: anaemia haemoglobin was categorised into anaemia; neutrophils to neutropenia; sensory neuropathy, motor neuropathy and neurotoxic effects were all grouped into neuropathy.

Table 38 compares the profile of AEs within each chemotherapy regimen and should not be used to compare toxicities across the different drug regimens. *Table 38* shows each drug regimen differs in toxicity profile in terms of percentage of AE.

Table 38 shows that the most common AEs are neutropenia, anaemia and leucopenia. Neutropenia is the top AE for VNB, PAX and DOC and granulocytopenia is the top AE for GEM and PEM. Neutropenia, leucopenia, granulocytopenia all describe a fall in the white blood count and so the common AEs are similar across all the chemotherapy drugs with the exception of GEF, which appears to have a different toxicity profile; the top AE for GEF is aminotransferase elevation. The highest proportion experiencing neutropenia (71%) was among those taking DOC.

TABLE 38 Weighted average[a] grade 3–4 AEs of 23 included trials

DOC + PLAT	GEF	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT
Neutropenia, 71.4%	Aminotransferase, elevation, 33.8%	Granulocytopenia, 48.8%	Neutropenia, 62.5%	Granulocytopenia, 37.9%	Neutropenia, 68.3%
Leucopenia, 43.5%	Appetite loss, 5.3%	Asthenia, 40.3%	Leucopenia, 31.9%	Blood transfusions, 26.9%	Leucopenia, 47.2%
Weakness, 16.0%	Rash/acne, 3.3%	Neutropenia, 36.4%	Weakness, 14.5%	Infection, 16.4%	Oedema, 24.0%
Pneumonitis, 11.5%	Toxic deaths, 3.1%	Thrombocytopenia, 34.6%	Cancer pain, 13.2%	Neutropenia, 15.1%	Anaemia, 19.3%
Anaemia, 11.2%	Diarrhoea, 3.1%	Anorexia, 27.0%	Nausea, 10.3%	Alopecia, 11.9%	Phlebitis, 15.7%
Asthenia, 10.2%	Neutropenia, 2.8%	Leucopenia, 20.1%	Anaemia, 10.0%	Leucopenia, 8.2%	Nausea/vomiting, 11.5%
Nausea, 9.9%	Pneumonitis, 2.6%	Transfusion, 18.5%	Lethargy, 9.4%	Thrombocytopenia, 8.1%	Vomiting, 10.3%
Vomiting, 9.8%	Fatigue, 2.5%	Alopecia, 17.2%	Thrombocytopenia, 8.3%	Anaemia, 7.0%	Nausea, 9.9%
Cancer pain, 8.4%	Infection, 1.8%	Weakness, 17.0%	Neuropathy, 7.9%	Fatigue, 6.7%	Asthenia, 9.4%
Infection, 7.5%	Anaemia, 1.6%	Anaemia, 16.5%	Vomiting, 7.4%	Nausea, 6.2%	Pain, 8.3%

a Weighted average = total number of events divided by total number of patients across trial arms.

Quality of life

Twelve trials[15,43–46,48,51,52,55,57,59,62,64] reported QoL outcomes and are listed in *Appendix 28*. It is surprising, given the importance of QoL, that 11[47,49,50,53,54,56,58,60,61,63,65] of the 23 trials do not report QoL data, including three trials[60,63,65] that were published in 2010. This could indicate outcome reporting bias, with trial authors failing to present results because they are not statistically significant. QoL was the primary outcome in two trials[45,62] and, in the trial by Gridelli *et al.*,[45] QoL data were assessed according to GEM + VNB compared with PLAT-based chemotherapy (the GEM + VNB combination is not included in this review). Meta-analysis was not performed for QoL data owing to limited data and variability in outcome assessment measures.

A number of instruments/tools that measure QoL were employed in the included trials. The EORTC QLQ-C30[29] and the lung cancer-specific module QLQ-LC13[30] were used in five trials, the LCSS[31] by three trials, and the FACT-L[32] questionnaire by three trials.[15,48,57,64]

Seven trials[48,45,51,52,55,59,62] reported no significant difference in QoL between treatment groups. Four trials[15,43,44,46,64] reported some significant differences between treatment groups for QoL; however, in one of these trials,[43] results after two cycles of chemotherapy favoured the PAX + CARB arm over the VNB + CIS arm, and results after four cycles favoured the VNB + CIS arm.

In one trial,[15,64] significantly more patients in the GEF group than in the PAX + CARB group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L questionnaire (odds ratio = 1.34; 95% CI 1.06 to 1.69; $p = 0.01$) and by scores on the Trial Outcome Index (TOI) (which is the sum of the physical well-being, functional well-being and lung cancer subscale scores of FACT-L; odds ratio = 1.78; 95% CI 1.40 to 2.26; $p < 0.001$).

In another trial[46] comparing GEM + CIS with PAX + CIS, no significant difference in global QoL was observed; however, a statistically and clinically significant overall improvement was observed for peripheral neuropathy and alopecia in the GEM + CIS arm compared with the PAX + CIS arm.

Patients treated with DOC + PLAT reported consistently improved global QoL compared with patients treated with VNB + CIS, who generally experienced deterioration in QoL in the trial by Fossella *et al*.[44]

In summary, PAX + PLAT may be associated with worse QoL for alopecia and peripheral neuropathy compared with VNB + PLAT and GEM + PLAT. GEM + PLAT may be associated with better QoL for peripheral neuropathy compared with PAX + PLAT and VNB + PLAT; however, there is a paucity of QoL data available to draw any firm conclusion.

Discussion

Summary of key results

Twenty-three trials that compared any first-line chemotherapy treatment currently licensed in Europe and recommended by NICE were included within the analyses; publication dates ranged from 2001 to 2010. Of the 20 multicentre trials, six had international centres.[15,44–46,59,61,64] All included trials were published in English. There are five Phase II trials,[51–53,56,58] 16 Phase III trials[15,43–46,48,49,54,55,57,59–65] and two trials[47,50] with phase undefined. Ten trials[15,43,44,53,57–62,64] were funded solely by pharmaceutical companies.

Evidence for the NSCLC population with squamous disease included 18 trials[43–62] (> 7000 patients and > 6000 deaths); these same 18 trials plus an additional two trials of PEM + PLAT with subgroup data provided evidence for the population with non-squamous disease. Three trials[15,63–65] conducted entirely within East Asian countries provided evidence for the NSCLC population with EGFR M+ status.

The PLAT-based doublets of DOC, GEM, PAX and VNB had relatively more data points for all outcomes than the newer PEM + PLAT regimen and GEF monotherapy. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and very good consistency across individual trials in the within-group comparisons.

Overall, the quality of the included RCTs was poorer than expected – there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials. In addition, it is generally agreed that RCTs typically include patients who are generally fitter and younger than patients receiving treatment in routine clinical practice and that outcomes from RCTs are not always of the same magnitude as those gained from routine care. Caution is therefore required when interpreting and comparing the results of these trials, in particular the results generated through meta-analysis and mixed-treatment comparison.

Non-small cell lung cancer population with squamous disease

The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion.

Only seven trials[45,47,51–54,56] were included in the PFS analysis and the majority of these trials used slightly different definitions of PFS. There was no evidence of any significant difference in PFS for GEM + PLAT compared with VNB + PLAT. There was insufficient evidence to conclude whether or not there were any statistically significant differences in PFS between the other third-generation chemotherapy comparators.

A further seven trials[43,44,46,49,50,58,60] reported results for the outcome TTP and there was no evidence of any statistically significant difference in TTP for GEM + PLAT compared with VNB + PLAT and GEM + PLAT compared with PAX + PLAT or between the other third-generation chemotherapy comparators.

Non-small cell lung cancer population with non-squamous disease

For patients with non-squamous disease there is evidence to suggest that PEM + PLAT increases OS compared with GEM + PLAT (direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00; mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98). There is no evidence to conclude that there is any statistically significant difference between any of the other chemotherapy treatments in terms of increasing OS for patients with non-squamous disease. Both the direct and indirect evidence suggest a potential advantage for GEM + PLAT compared with VNB + PLAT in terms of OS; however, this advantage is not statistically significant. Both the direct and indirect evidence suggest a potential advantage for DOC + PLAT compared with VNB + PLAT in terms of OS; however, this advantage is borderline statistically significant (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03). The mixed-treatment comparison 1 analysis shows a statistically significant difference between PAX + PLAT and DOC + PLAT (HR = 0.79; 95% CI 0.66 to 0.93); however, the direct meta-analysis 1 was not significant.

Epidermal growth factor receptor mutation-positive population

For patients with EGFR M+ status, there is no statistically significant difference in OS between GEF compared with PAX + PLAT and between GEF compared with DOC + PLAT. There is evidence of a statistically significant improvement in PFS with GEF compared with DOC + PLAT. Although there is also evidence of a statistically significant improvement in PFS with GEF compared with PAX + PLAT the significant heterogeneity between trials means the PFS results should be viewed with caution.

Generalisability of results

A limitation to this review is the generalisability of the patients in the included trials to the population with NSCLC in the UK. In the earlier trials of third-generation chemotherapy drugs, patients with NSCLC were treated as a generic group when in fact it is now accepted that they are a mixed population comprising patients with squamous and non-squamous disease. Earlier trials that assessed the clinical effectiveness of the third-generation chemotherapy drugs did not differentiate on factors such as histology or genetic markers. The mix of patient population is now expected to be taken into consideration at the time of trial design as demonstrated in the PEM and GEF trials. Making comparisons across the six available first-line chemotherapy treatments is therefore limited by the comparability of the treatment populations in the published trials.

In addition, it is questionable whether or not the results from four trials based entirely in East Asian populations[50–52,57] are generalisable to UK clinical practice. The evidence relating to the EGFR M+ populations is based entirely on patients within East Asian populations. There are no relevant UK-based trial data for patients with EGFR M+ status. Evidence suggests that East Asian populations with NSCLC have a more favourable prognosis compared with non-East Asian populations.[82] Although EGFR mutation rates are likely to be quite different in different countries, actual response to chemotherapy may not differ in patients with the same mutation status.

Strengths and limitations

This is the first comprehensive systematic review and economic evaluation of all first-line chemotherapy options that are currently licensed for use in the UK and recommended by NICE for patients with advanced NSCLC. This includes PLAT-based doublets with DOC, GEM, PAX, PEM and VNB and also GEF monotherapy. This review highlights that research in this area is evolving rapidly with advances seen in relation to histology and genetic subgroups within the NSCLC population.

There was no direct evidence identified for six different comparisons of chemotherapy drugs which was a limitation; however, a particular strength of this review is that it is the first review to use indirect

evidence from mixed-treatment comparison analyses to compare relative treatment effects across all six chemotherapy regimens. In general, there was consistency between the survival outcome data from direct meta-analyses and mixed-treatment comparison analyses and also homogeneity across the individual trials within the drug group comparisons. Evidence used in those comparisons which demonstrate borderline statistically significant results should be treated with caution and used to indicate possible differences in chemotherapy treatments that should then be assessed by a formal trial (i.e. viewed as research generating) and should not be used alone to justify changes in clinical practice.

This report was limited in its analyses of AEs mainly because trials varied in the way AEs were defined, measured and reported. For example, grade 3 and 4 AEs were reported separately or in aggregate. For this reason, where trials reported within-trial significant differences between chemotherapy treatment groups, these differences were highlighted in the report, although this approach may be hampered by the potential for selective reporting bias by the authors. AE data are often sparse with wide CIs, which means that individual trials lack the power to detect significant differences.

This report highlights the top 10 AEs that occurred within each chemotherapy regimen and are produced by weighted average grade 3–4 AEs which are calculated by the number of events related to the toxicity in all arms from all included trials of each chemotherapy regimen, divided by the number of patients who experience these events in all arms. However, this approach loses all the benefits of randomisation and a comparative control group because it splits arm-level data. This approach does not provide information about the comparative harms of chemotherapy (which would assist in balancing the potential benefit and risk of each chemotherapy regimen) and it is merely intended to highlight the different toxicity profiles of the six chemotherapy regimens. AE data were not reported by the three populations used to assess survival data or for cost-effectiveness analysis (CEA); patients with squamous and non-squamous disease.

Further research is required regarding the clinical significance of any of the reported AEs, also the significance to patients in terms of QoL and any differences in terms of costs. AE reporting needs to be standardised and reported consistently across trials if future comparisons are going to be possible.

Overall survival is an important outcome in deciding which chemotherapy drug a patient should receive, but this needs to be considered alongside the toxicity of chemotherapy therapy and the symptomatic benefits of therapy (QoL). A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy treatment and early deaths associated with NSCLC. However, a British Thoracic Oncology Group Phase III trial[83] [British Thoracic Oncology Group Trial 2 (BTOG2)] comparing GEM (1250 mg/m^2 day 1 and day 8) with either CIS 80 mg/m^2, CIS 50 mg/m^2 or CARB area under curve (AUC) 6 is the largest study to date to collect QoL data on patients with NSCLC. QoL was measured at each chemotherapy cycle and follow-up visit using standard, validated questionnaires. More than 8000 questionnaires were returned from 1363 patients with compliance around 90% during the treatment period. This trial shows that it is feasible to collect QoL data in patients with PS 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting.

Carboplatin and CIS were grouped together and treated as similar for the clinical effectiveness analyses, based on NICE guidelines[7] which recommend that either CARB or CIS may be administered depending on the balance of toxicity, efficacy and convenience. CIS and CARB do differ in their toxicity profiles and differ in the mode of administration particularly in the time required for delivery. The hydration needed for CIS, which requires more hospital time than CARB, deters some clinicians from using it. There is variation between oncologists (and hence variation in usage by centre) as to which PLAT is preferred. The results of recent meta-analyses[84,85] suggest that CIS delivers greater efficacy than CARB, and subsequently use of CIS has increased, but overall clinical practice in the UK is still split between the two PLATs. CIS and CARB have, in general, been considered interchangeable in terms of efficacy because neither is consistently superior in terms of OS. However, the efficacy of CARB and CIS may vary according to the specific type of

chemotherapy drug it is combined with and the histology and disease stage of the patient. The BTOG2[86] aimed to establish the optimal CIS dose and whether or not CARB can be effectively substituted for the CIS at this dose; and will help to clarify the evidence regarding the relative efficacy of CIS and CARB in terms of survival, QoL and costs associated with each drug and its delivery. Publication of results is expected in 2013.

The results in this report are based entirely on the analysis of published data from Phase II and Phase III clinical trials. It is well known that patients in such trials are not necessarily representative of patients seen in UK clinical practice. The National Lung Cancer Audit has been collecting activity, performance and outcome data since 2005 and provides data on treatment rates, including chemotherapy, for every managing hospital trust in the UK, by cell type, stage, age and PS of the patients. What it has not been able to do is collect data on the specific drug regimens or the number of chemotherapy cycles being administered. New initiatives to collect data related to UK patients and the treatment they receive are now in place through the emergence of the National Cancer Intelligence Network[87] and the National Cancer Data Repository that underpins it. The National Systemic Anti-Cancer Therapy (SACT) data set became operational on the 1 April 2012 and will enable much more detailed analyses of treatment and outcomes in this patient population. Thus, we will soon have access to detailed information on the precise chemotherapy (and targeted chemotherapy) regimens being used, together with data on age, cell type, stage of disease and PS, allowing for very detailed observational audits of management and outcomes at a population level. It will also be feasible to include health economic data into such future analyses. We would strongly endorse the development of initiatives of this kind in the effort to provide data that can more accurately define the true cost–benefit ratio of treatment interventions in this patient population.

A limitation of this review is that there is a very large volume of related literature in this field and so pragmatic decisions had to be taken about the inclusion criteria and the focus of the data analyses; therefore, the methods employed in this review differ slightly from the methods described in the original review protocol. We restricted the analysis to papers published from 2000 onwards and decided to include only chemotherapy drugs that are currently licensed and recommended by NICE for use in patients with NSCLC; we believe this to be the best management of the data in order to make the result of the review useful to clinicians.

Another potential limitation of this report is that the elderly population with NSCLC may be under-represented in the included trials. The majority of trials have an upper age limit, whereas in clinical practice there are substantial proportions of treated patients > 75 years of age. The majority of trials also focus on fitter populations with less comorbidity (which may include a larger proportion of elderly patients) than the average UK patient with NSCLC. In addition, we excluded single-agent regimens of DOC, GEM, PAX and VNB. Although the included chemotherapy drugs are not licensed for single-agent use, NICE[7] states that DOC, GEM, PAX and VNB can be used for single-agent use if patients are intolerant of a PLAT-based doublet regimen, and this may include a larger proportion of elderly patients. Trials of single-agent regimens have focused on the elderly population, for example the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS)[88] demonstrated a significant survival advantage for elderly patients taking single-agent VNB compared with BSC. The Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial[89] showed that VNB + GEM did not improve survival compared with single-agent use of VNB and single-agent use of GEM in elderly patients with NSCLC. The elderly are less likely to have chemotherapy treatment in clinical practice in the UK, which is not explained by poorer PS or increased comorbidity.[90] Authors of a LUCADA indicate that further work is warranted to determine how far this can be explained by patient preference, appropriate physician judgement and physician prejudice.[91]

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review of the economic literature was conducted to identify the existing evidence assessing the cost-effectiveness of first-line chemotherapy for patients with advanced and/or metastatic NSCLC. The criteria shown in *Table 39* were used to identify the relevant studies for inclusion in the review. The search included a combination of terms (e.g. carcinoma, non-small-cell lung, economics, costs and cost analysis, effectiveness) and was limited to English-language articles. The electronic databases, including MEDLINE, EMBASE and The Cochrane Library (Issue 3, July 2010), were searched for the period from January 1980 to August 2010. All references were exported to the EndNote® version X4. Full details of the search strategies are available in *Appendix 29*. Two reviewers independently screened all titles and abstracts of papers identified in the search. Discrepancies were resolved by discussion with involvement of a third reviewer where necessary.

Time frame of searching

The electronic searches for the cost-effectiveness review were originally developed for the same time frame as the clinical-effectiveness review (1980–2010); however, it was later decided to include only those trials published after the year 2000 as active chemotherapy treatments for patients with lung cancer have been evolving rapidly since this date. The clinical effectiveness and cost-effectiveness review of lung cancer treatments by Clegg *et al.*[39] was published in May 2001 and included economic evaluations up to and including 2000. None of the individual studies identified by Clegg *et al.*[39] are therefore included in this systematic review.

TABLE 39 Inclusion and exclusion criteria

Inclusion criteria	
Evaluation design	Full economic evaluations that consider both costs and consequences (CEA, CUA and cost–benefit analysis)
Patient population	Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC
Interventions	Any first-line chemotherapy treatment currently licensed: • PLAT-based chemotherapy (CARB or CIS) in combination with DOC, GEM, PAX, VNB or bevacizumab (Avastin®, Roche Products Limited and Roche Diagnostics Limited) • PEM + CIS • Single-agent therapies including ERL, GEF and cetuximab
Comparators	It is envisaged that the interventions will be compared with active therapy as described above
Outcomes	Incremental cost per LYG Incremental cost per quality-adjusted LYG
Exclusion criteria	
Other considerations	Only studies published post 2000 in full and with English-language abstracts will be included
Trial design	CMAs are excluded from the review as there have not been any clinical equivalence trials conducted in this area and so any CMA would involve the questionable assumption of clinical equivalence

CMA, cost-minimisation analysis; CUA, cost–utility analysis.

Identification of economic evaluations

A total of 1510 publications were identified as a result of the electronic searches. During stage 1, these studies were screened and duplicated papers were removed. In stage 2, titles and abstracts were screened and 15 papers[39,92–105] were selected for potential inclusion in the review. Inclusion and exclusion criteria were applied to these 15 full papers and seven reports[39,93–95,97,99,101] were included in the review. The flow diagram in *Figure 24* shows the number of reports available at each stage of the inclusion process.

The lung cancer costing model discussed in the two publications by Clegg *et al*.[39,93] are focused primarily on chemotherapy compared with BSC. However, as they do include two chemotherapy versus chemotherapy comparisons as part of their detailed economic analysis, all data have been extracted and included in this review for information purposes only.

Relevant data were extracted from six evaluations from seven included publications[39,93–95,97,99,101] into evidence tables (see *Tables 42–45*). All data were checked for accuracy by a second reviewer. The eight full-text reports[92,96,98,100,102–105] that were excluded during the latter stages of the inclusion process are listed in *Table 40* alongside reasons for exclusion. Of these eight trials, five[96,102–105] were excluded as they were cost-minimisation analyses (CMAs) only. CMAs were explicitly excluded from the literature review as there are no published results from clinical equivalence trials between chemotherapy regimens for patients with NSCLC in the first-line setting to support such an analysis.

The quality of the reports was assessed using the 35-item list described by Drummond and Jefferson,[106] the results of the quality assessment exercise are shown in *Table 41*. All of the reports are of good/reasonable methodological quality. They typically include the key components of a credible economic evaluation. The key methodological weaknesses include the following: a lack of detail on costs (e.g. no separation of quantity of resources consumed from unit costs); non-explicit statement of length of time horizon or discount rate used; and, in some cases, the authors did not provide disaggregated outcomes or carry out incremental analyses. The main weaknesses of the reports included in the review stem not from their quality but from their limited relevance to UK decision-making. This is a result of the comparisons considered and choice of incremental cost-effectiveness ratio (ICER) rarely being cost per QALY gained.

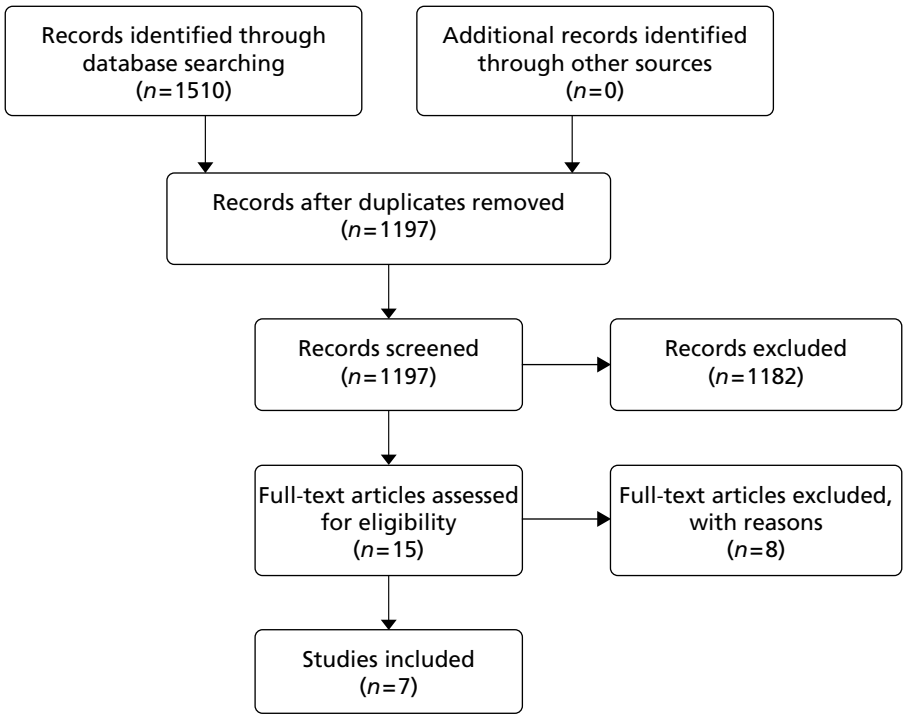

FIGURE 24 Flow diagram at different stages.

TABLE 40 Excluded reports

Report	Reason for exclusion
Lievens 2005[98]	One comparator was radiotherapy
Rubio-Terrés 2002[104]	CMA
Pimentel 2006[103]	CMA
Neubauer 2010[100]	Comparators were a compound of first- and second-line treatments
Chen 2002[92]	CEA is only a costing exercise
Manidiakis 2010[105]	CMA
Novello 2005[102]	CMA
Le Lay 2007[96]	CMA

CMA, cost-minimisation analysis.

TABLE 41 Quality assessment

Checklist item	Clegg 2001/2[39,93]	Dooms 2006[94]	Klein 2009[95]	Lees 2002[97]	Maniadakis 2007[99]	Neymark 2005[101]
The research question is stated	Y	Y	Y	Y	Y	Y
The economic importance of the research question is stated	Y	Y	Y	Y	Y	Y
The viewpoint(s) of the analysis are clearly stated and justified	Y	Y	Y	NC	Y	Y
The rationale for choosing the alternative programmes or interventions compared is stated	Y	Y	Y	Y	Y	Y
The alternatives being compared are clearly described	Y	Y	Y	Y	Y	Y
The form of economic evaluation used is stated	Y	Y	Y	NC	Y	Y
The choice of form of economic evaluation is justified in relation to the questions addressed	Y	Y	Y	NC	Y	Y
The source(s) of effectiveness estimates used are stated	Y	Y	Y	Y	Y	Y
Details of the design and results of effectiveness trial are given (if based on a single trial)	Y	Y	Y	Y	Y	Y
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness trials)	Y	NA	Y	Y	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	Y	Y	Y	Y	Y	Y
Methods to value health states and other benefits are stated	Y	Y	Y	NA	NA	NA
Details of the subjects from whom valuations were obtained are given	Y	NC	Y	Y	NA	NA
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA

continued

TABLE 41 Quality assessment (*continued*)

Checklist item	Clegg 2001/2[39,93]	Dooms 2006[94]	Klein 2009[95]	Lees 2002[97]	Maniadakis 2007[99]	Neymark 2005[101]
The relevance of productivity changes to the study question is discussed if included	NA	Y	NA	NA	NA	NA
Quantities of resources are reported separately from their unit costs	Y	Y	N	N	Y	Y
Methods for the estimation of quantities and unit costs are described	Y	NC	NC	N	Y	Y
Currency and price data are recorded	Y	Y	Y	Y	Y	Y
Details of currency price adjustments for inflation or currency conversion are given	Y	Y	Y	Y	N	NC
Details of any model used are given	Y	NA	NC	N	NA	NA
The choice of model used and the key parameters on which it is based are justified	Y	NA	NC	N	NA	NA
Time horizon of costs and benefits is stated	NA	Y	Y	NC	N	Y
The discount rate(s) is stated	NA	NA	NA	NA	NC	NC
The choice of rate(s) is justified	NA	NA	NA	NA	NC	NC
An explanation is given if costs or benefits are not discounted	Y	Y	N	Y	NC	NO
Details of statistical tests and CIs are given for stochastic data	Y	N	N	Y	Y	Y
The approach to sensitivity analysis is given	Y	Y	Y	Y	Y	Y
The choice of variables for sensitivity analysis is justified	Y	Y	Y	NC	NA	Y
The ranges over which the variables are varied are stated	Y	Y	Y	NC	NA	Y
Relevant alternatives are compared	Y	Y	Y	Y	Y	Y
Incremental analysis is reported	Y	Y	Y	NC	Y	NO
Major outcomes are presented in a disaggregated as well as aggregated form	Y	Y	Y	NC	NC	Y
The answer to the study question is given	Y	Y	Y	Y	Y	Y
Conclusions follow from the data reported	Y	Y	Y	Y	Y	Y
Conclusions are accompanied by the appropriate caveats	Y	Y	Y	Y	N	Y

N, no; NA, not applicable; NC, not clear; Y, yes.

Study characteristics and model overview

Three[97,99,101] of the seven included studies are CEAs. Two papers[39,93] are based on the use of three different economic models: a pair-wise comparison between the regimens or BSC (model 1), a CMA (model 2) and a CEA with BSC as the comparator (model 3); only model 1 included a chemotherapy compared with chemotherapy comparison. The study by Klein *et al.*[95] presents results from both a CMA and a cost–utility analysis (CUA) and the study by Dooms *et al.*[94] is a CUA.

Klein *et al.*[95] uses a Markov framework with an initial simple decision tree covering a 6-month period followed by three 6-month cycles. The other studies use simple decision trees with time horizons of ≤ 1 year in four trials,[39,93,94,97] 3 years[101] and 40 months.[99] Most of the economic evaluations have short time frames; this is because they are based on clinical trials with mean OS estimates of approximately 10 months. All of the reports, but one,[94] have been conducted using a third-party payer perspective taking account of direct costs only. Dooms *et al.*[94] adopts a societal perspective using direct costs and costs related to travel expenses. Three[39,93,97] are UK based, one is set in Belgium,[94] one in Greece,[99] one in the Netherlands[101] and one in the USA.[95]

Four reports[39,93,94,99] were funded from public grants or from university funds, two[95,97] were funded by a pharmaceutical company and one[101] was funded jointly by a pharmaceutical company and several hospitals.

The comparators used in each of the studies and detailed information about design and trial characteristics are presented in *Table 42*.

Model inputs and data sources

Costs were typically divided into the following categories: costs of drug administration, side effects costs, acquisition costs of drugs, costs of BSC, costs of tests/investigations; and the costs of travel expenses were considered in the only study[94] using a societal perspective. The sources included public costs databases, hospital costing data and Medicare reimbursement rates. In general, costs were extracted from publicly available documents, which adds transparency to the costing approaches described in the studies. The economic models, cost item and the sources used are summarised in *Tables 43* and *44*.

The most commonly used efficacy outcome was survival time with median survival time (MST) used in four[39,93,97,101] and OS used in three.[94,97,99] Response rates or ORRs were also used. All efficacy data used in the included studies are shown in *Table 45*. Sources of efficacy data are varied; a single clinical trial was used in five[94,95,97,99,101] of the seven reports and the remaining two[39,93] took data from a collection of trials using a mixed-treatment comparison to summarise the data.

Five studies used data from trials[39,93–95,99] and used life-year saved (LYS) or LYG as the primary health outcome, whereas two used QALYs.[4,116] Different approaches for calculating QALYs were used in each of the latter of these studies. Klein *et al.*[95] adopted a CUA approach and used utility values from the published study by Naffes *et al.*[116] to calculate the QALYs gained in each regimen. Dooms *et al.*[94] used one item from the LCSS QoL instrument and transformed this into a corresponding utility value; these utilities were then combined with the survival data from a RCT in order to obtain QALYs. Several studies expressed their incremental ratios in terms of cost per progression-free life-year, cost per tumour response or costs to improve mean survival.

Results and sensitivity analysis

Tables 46 and *47* show the cost-effectiveness results, sensitivity analyses and conclusions of the reports. The results of the economic evaluation by Clegg *et al.*[39,93] reveal that any chemotherapy regimen is cost-effective (vs BSC) at a threshold of £30,000 per LYS except PAX. In the chemotherapy versus chemotherapy comparisons, GEM + CIS dominates GEM and VNB + CIS is cost-effective when compared with VNB. The conclusion of the authors is that depending on the assumptions used, the new drugs range from being

TABLE 42 Study characteristics

Study	Source	Type of study	Interventions	Study population	Country	Duration of study	Industry/author affiliation
Clegg 2001/2[39,93]	Full text	Model 1: Pair-wise comparisons from published trials Model 2: CMA Model 3: CEA (vs BSC)	PAX, DOC, GEM, VNB, BSC	Patients with NSCLC	UK	< 1 year	This study was supported by the NHS R&D HTA programme
Dooms 2006[94]	Full text	CUA	GEM, CIS + VIN	Patients with symptomatic advanced NSCLC	Belgium	< 1 year	The funding source is not stated. Authors affiliation: Leuven University
Klein 2009[95]	Full text	CEA/CUA	CIS + PEM, CIS + GEM, CARB + PAX, CARB + PAX + BEV	Patients with symptomatic advanced NSCLC	USA	2 years	Authors were contracted by Eli Lilly and Company and to conduct the research or work in Eli Lilly and Company
Lees 2002[97]	Full text	CEA	(1) GEM + BSC vs BSC (2) GEM + CIS vs ETOP + CIS vs MIC + CIS vs MVP (3a) GEM + CIS vs taxane/PLAT regimens (3b) GEM + CIS vs VNB	Patients with NSCLC	UK	1 year	This study was carried out with a research grant from Eli Lilly and Company
Maniadakis 2007[99]	Full text	CEA	DOC + GEM DOC	Patients with advanced/metastatic NSCLC	Greece	40 months	Public health-care members. No conflict of interest or funding from industry declared
Neymark 2005[101]	Full text	CEA	CIS + PAX CIS + GEM GEM + PAX	Patients with advanced/metastatic NSCLC	Netherlands	3 years	Authors are staff from several Medical centers around the Netherlands. The study was partially supported by Bristol-Myers Squibb and Eli Lilly and Company (provision of drugs used in the RCT)

BEV, bevacizumab; ETOP, etoposide; HTA, Health Technology Assessment; MIC, mitomycin, ifosfamide and cisplatin; MVP, mitomycin, vinblastine and cisplatin; R&D, research and development; VIN, vinblastine.

TABLE 43 Economic model and costs

Study	Type of model	Perspective	Model assumptions	
			Outcomes	Costs and resource use
Clegg 2001/2[39,93]	Three simple decision trees	Third-payer perspective	No RCTs directly compared two or more regimens in terms of QoL; thus, side-by-side comparisons cannot be made Whether or not one cycle of a regimen is equivalent to one cycle of another remains unclear and it is addressed in the SA PAX doses varied markedly between trials and so several regimens were considered Data on effectiveness were pooled using mixed-treatment comparison	Costs of antiemetic and diuretics were negligible and were excluded from the analysis Cost of administration of drug in case of AEs were £500 (expert advice) Costs from published and unpublished data
Dooms 2006[94]	Simple decision tree	Societal perspective	No differences in survival were observed between the two regimens but differences in QoL and clinical benefit were observed. Based on this finding, authors decided to carry out CUA using QALYs QALYs have been estimated using a VAS score from the LCSS QoL instrument. This VAS score was considered to be a reasonable alternative to the VAS thermometer score in the EQ-5D instrument	Direct non-medical costs = travel expenses Indirect costs are not taken into account because they are assumed to be equal in both groups Second-line chemotherapy and radiotherapy did not show any significant difference between groups and were not taken into account Costs of diagnostic procedures and the expenditure at the end of the treatment period were unavailable and no real differences were assumed between the two arms
Klein 2009[95]	Semi-Markov model with three 6-month cycles	US payer	Health states of partial and complete response were not reached until the beginning of the third and fourth cycle, respectively Side effects probabilities assumed to be independent of the health state and response, and progression probabilities assumed to be independent of side effects Dose reductions/delays between chemotherapy cycles were not modelled State transition probabilities beyond the first year were assumed to be the same for all initial treatments	As long as the overall proportions of AEs are correct and AE costs are independent of treatment or disease costs, not altering AE probabilities by health state should have no effect on cost results Costs and utilities for the health states without chemotherapy were assumed to be equivalent regardless of the first-line treatment used

continued

TABLE 43 Economic model and costs (*continued*)

Study	Type of model	Perspective	Model assumptions	
Lees 2002[97]	Simple decision tree	UK NHS	All outcomes are taken from head-to-head clinical trials	Only direct NHS health costs were included Wastage was incorporated into the analyses
Maniadakis 2007[99]	Simple decision tree	Greek NHS	Data on several clinical outcomes were collected; only mean survival has been used in the CEA	Only (Greek) NHS direct costs are included Cost of chemotherapy in each cycle is calculated by multiplying the exact dose given by cost per mg. No drug wastage
Neymark 2005[101]	Simple decision tree	Third-party payer	Antiemetic agent doses selected by examining the literature	Costs of drugs are based on the amount reimbursed by the health insurance firm

SA, sensitivity analysis; VAS, visual analogue scale.

TABLE 44 Cost items and data sources

Study	Cost items and cost data sources	Currency and currency year	Discount rate
Clegg 2001/2[39,93]	Administration of drugs and side effect costs (Scottish Health Purchasing Information Centre; Scottish Health Service Cost´s 'blue book'; Ninewells Hospital) Chemotherapy counselling (Scottish Health Purchasing Information Centre; Scottish Health Service Cost´s 'blue book'; Southampton General Hospital) Costs of drugs (BNF) BSC costs (case notes of patients published elsewhere and checked with the data from South-East Lung Trial)	£/1999–2000	NA
Dooms 2006[94]	Costs of chemotherapy drugs, concomitant medications, outpatient admissions and inpatient hospitalisation during chemotherapy (Leuven University Hospital Pharmacy) Direct non-medical costs related to the travel expenses Resource-cost data were calculated from the actual data collected during the prospective clinical trial	€/2000	NA
Klein 2009[95]	NSCLC-related direct health-care costs including chemotherapy, costs of pre-medication, administration of chemotherapy, laboratory monitoring, treating common AEs, subsequent therapies, direct care for disease-related morbidity, and end-of-life care (Medicare reimbursement rates; Pharmetrics paid claims database[107])	US$/NS	NA
Lees 2002[97]	Costs associated with chemotherapy acquisition and use of concomitant medications (BNF 40[108]) Hospitalisation (2000 UK National Schedule of Reference Costs[109]) Infusion and visits to health professionals (UK-based source of unit costs in health care; University of Kent at Canterbury[110]) Radiotherapy (previous economic evaluation Bagust 1999[111])	£/2002	NA
Maniadakis 2007[99]	Treatment costs: initial chemotherapy, concomitant medications, radiotherapy, diagnostic and laboratory testing, any hospitalisation and resources necessary for the treatment of AEs, follow-up visits and second-line chemotherapy (Greek national sources and database from the University General Hospital Heraklion)	€/2005	NS
Neymark 2005[101]	Hospital overnight stay (daily allowance); day clinic stay (daily allowance); outpatient specialist consultations; transfusions (red blood cells); transfusions (platelets); pre-medication before PAX; antiemetics/CIS regimens (per cycle); antiemetics/non-CIS regimens (per cycle); trial treatments (radiotherapy, second line); chemotherapy (second line); surgery (second line) All cost data collected from: College Tarieven Gezondheidszorg (CTG);[112] Tarieven voor Medisch Specialisten; Tarieflijst Instellingen for Hospitals; *Farmacotherapeutisch Kompas*[113]	€/2002	NS

NA, not applicable; NS, not significant.

TABLE 45 Efficacy and health outcomes

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Discount rate
Clegg 2001/2[39,93]	Median number of cycles MST	Collection of 33 trials from the systematic review conducted by the authors	LYS	Collection of 33 trials found in a systematic review conducted by the authors	NA
Dooms 2006[94]	ORR OS Clinical benefit	Data were collected from a prospective Phase III RCT (Vansteenkiste 2001[114])	QALYs LYS	Patient responses to one item in the LCSS QoL instrument (from patients in RCT[114]) were converted to a single utility value	NA
Klein 2009[95]	TRR Progression rate	Data were obtained from a head-to-head trial (Scagliotti 2008[61]) and from a mixed-treatment comparison presented by Vansteenkiste *et al.* in 2008[115] in Dresden (Proceedings of the Internal Thoracic Oncologic Congress)	LYG QALYs	Utility values were calculated using an algorithm by Nafees 2008[116]	NA
Lees 2002[97]	(1) PFS, OTR and TTR (2) OS, PFS, MST and OTR (3a) OS, RR and TTP (3b) MST and RR	(1) Anderson 2000[117] (2) Cardenal 1999,[118] Crino 1999[119] and results presented in the World Lung Conference Tokyo 2000 (3a) Schiller 2000[47] (3b) Comella 2000[120]	(1) PFS, TTR and OTR (2) OS, PFS, MST and OTR (3a) OS, RR and TTP (3b) MST and RR	(1) Anderson 2000[117] (2) Cardenal 1999,[118] Crino 1999[119] and results presented in the World Lung Conference Tokyo 2000 (3a) Schiller 2000[47] (3b) Comella 2000[120]	NA
Maniadakis 2007[99]	TTP Number of deaths Response rates and duration OS	Multicenter Phase III RCT conducted by the HORG	LYS	Multicenter Phase III RCT conducted by the HORG	NS
Neymark 2005[101]	MST	Data were collected prospectively as an integrated part of the clinical trial presented in the paper	None is stated apart from the use of bootstrapping techniques to get CI and ICER	NS	NS

HORG, Hellenic Oncology Research Group; NA, not applicable; NS, not significant; OTR, overall tumour response; TRR, time to treatment response; TTR, time to radiotherapy.

TABLE 46 Cost-effectiveness results and conclusions

Study	Total costs	Total outcomes	ICERs	Conclusion
Clegg 2001/2[39,93]	**Average cost per patient model 1:** BSC vs GEM: £3342 vs £4132 BSC vs VNB: £3342 vs £2812 GEM + CIS vs VNB + CIS: £3943 vs £4420 BSC vs PAX: £3342 vs £8293 BSC vs DOC: £3342 vs £5040 VNB vs VNB + CIS: £3675 vs £4448 BSC vs DOC (75) vs DOC (100): £3342 vs £4365 vs £5040 DOC (75) vs DOC (100): £4365 vs £5040 **Average cost per patient models 2 and 3:** BSC £3342; GEM £4132; GEM + CIS £6321; VNB £3675; VNB + CIS £4736; PAX £8293; PAX (135) + CIS £6304; PAX (175) + CIS £7550; PAX (250) + CIS £8147; DOC £5040; DOC (2L) £4365	**MST (months) and LYS model 1:** BSC vs GEM (MST; LYS): 5.9; 0.49 vs 5.7; 0.48 BSC vs VNB (MST; LYS): 4.8; 0.40 vs 6.5; 0.54 GEM + CIS vs VNB + CIS (MST; LYS): 8.1; 0.68 vs 6.7; 0.56 BSC vs PAX (MST; LYS): 4.8; 0.40 vs 6.8; 0.57 BSC vs DOC (MST; LYS): 5.7; 0.48 vs 6.0; 0.50 VNB vs VNB + CIS (MST; LYS): 7.2; 0.60 vs 9.2; 0.77 BSC vs DOC (75) vs DOC (100) (MST; LYS): 4.6; 0.38 vs 7.5; 0.63 vs 5.9; 0.49 DOC (75) vs DOC (100) (MST; LYS): 5.7; 0.48 vs 5.5; 0.46 **Model 2:** Assumes equal efficacy **Median survival model 3:** BSC 5.24; GEM 6.9; GEM + CIS 8.80; VNB 7.06; VNB + CIS8.45; PAX 6.51; PAX (135) + CIS 9.40; PAX (175) + CIS 8.81; PAX (250) + CIS 10.00; DOC 6.00; DOC (2L) 5.94 **LYS model 3:** BSC 0.44; GEM 0.58; GEM + CID 0.73; VNB 0.59; VNB + CID 0.70; PAX 0.54; PAX (135) + CIS 0.78; PAX (175) + CIS 0.73; PAX (250) + CIS 0.83; DOC 0.50; DOC (2L) 0.49	**Incremental cost per LYS model 1:** BSC vs GEM: GEM dominated BSC vs VNB: BSC dominated GEM + CIS vs VNB + CIS: VNB ± CIS dominated BSC vs PAX: £29,704 (PAX) BSC vs DOC: £67,926 (DOC) VNB vs VNB + CIS: £4638 (VNB ± CIS) BSC vs DOC (75) vs DOC (100): £4234 (DOC 75); DOC (100) dominated DOC (75) vs DOC (100): DOC (100) dominated **Incremental cost per LYS model 3:** (vs BSC): GEM £5690; GEM + CIS £10,041; VNB £4091; VNB + CIS £5206; PAX £46,610; PAX (135) + CIS £8537; PAX (175) + CIS £14,124; PAX (250) + CIS £12,104; DOC £26,707; DOC (2L) £17,546	The new drugs for NSCLC extend life by only a few months compared with BSC, but appear to do so without net loss in QoL and at a cost per LYG that is much lower than for many other NHS activities. Depending on assumptions used these new drugs range from being cost-effective, as conventionally accepted, to being cost saving

continued

TABLE 46 Cost-effectiveness results and conclusions (*continued*)

Study	Total costs	Total outcomes	ICERs	Conclusion
Dooms 2006[94]	CIS + VIN: €4502 per patient GEM: €6024 per patient	**LYS:** CIS + VIN: 0.53; GEM: 0.68 **QALYs:** CIS + VIN: 0.18; GEM: 0.29	**ICER:** €13,836/QALY	Although the least expensive strategy is CIS + VIN, the greater clinical benefit of GEM balances its higher cost and generates an acceptable incremental cost–utility ratio
Klein 2009[95]	CIS + GEM: $61,535 CARB + PAX: $50,283 CIS + PEM: $66,606 CARB + PAX + BEV: $90,004	**LYG:** CIS + GEM: 0.9102 CARB + PAX: 0.8882 CIS + PEM: 0.9587 CARB + PAX + BEV: 1.0379 **QALYs:** CIS + GEM: 0.4661 CARB + PAX: 0.4469 CIS + PEM: 0.4943 CARB + PAX + BEV: 0.5260	**Incremental (ONLY NS) CARB + PAX + BEV to CIS + PEM:** $337,179/LYG; $1,006,065/QALY **Incremental CIS + PEM to CIS+GEM:** $104,577/LYG; $179,597/QALY **Incremental CIS + PEM to CARB + PAX:** $231,291/LYG; $343,870/QALY	Compared with commonly used and reimbursed regimens for first-line chemotherapy in advanced NSCLC, PEM + CIS may be considered cost-effective, particularly in patients with NS cell histology. This analysis emphasises the importance of histology in identifying the appropriate patients for PEM + CIS first-line chemotherapy
Lees 2002[97]	(1) GEM + BSC: £5502; BSC: £3861 (2) GC: £4142–5084; EP: £3762; MIV: £4481; MVP: £4005 (3a) GEM + CIS: £5537; PAX + CIS: £9043; PAX + CARB: £8444; DOC + CIS: £5779 (3b) GEM + CIS: £4477; VNB + CIS: £5048	(1) TTR (days) GEM + BSC: 288; BSC: 173. PFS (years) GEM + BSC: 0.789; BSC: 0.474. OTR (%): GEM + BSC: 18.5; BSC: 0.0 (2) EP: PFS (years): 0.358. OTR (%): 21.9. MIC: OTR (%): 27.6. MVP: OS (%): 17. OTR (%): 36.7. GEM + CIS: PFS (years): 0.575. OTR (%): 39.6–54. OS (%): 36 (3a) RR (%): GEM + CIS: 21; PAX + CIS: 21.3; DOC + CIS: 17.3; PAX + CARB: 15.3. OS (years): GEM + CIS: 0.375; PAX + CIS: 2.92; DOC + CIS: 0.275; PAX + CARB: 0.3 (3b) MST (weeks): GEM + CIS: 42; VNB + CIS: 35. RR (%): GEM + CIS: 30; VNB + CIS: 25	(1) GEM + BSC vs BSC: Cost per progression-free life-year: £5228. Cost per tumour response: £8873 (2) GEM + CIS vs EP: Cost per progression-free life-year: £1751. Cost per tumour response: £2032. GEM + CIS vs MIC: Cost per tumour response: £5169. GEM + CIS vs MVP: Cost per % gain in 1-year survival: £5681. Cost per tumour response: £6240 (3a) Incremental costs only: GEM + CIS vs PAX + CIS: –£3506; GEM + CIS vs PAX + CARB: –£2907; GEM + CIS vs DOC + CIS: –£242 (3b) GEM + CIS vs VNB + CIS: –£571	GEM alone or in combination with CIS was assessed to be a cost-effective or cost-saving therapy when compared with BSC, standard and novel chemotherapy. Chemotherapy regimens containing GEM therefore represent good value for money and an efficient use of health-care resources in the treatment of advanced NSCLC

Study	Total costs	Total outcomes	ICERs	Conclusion
Maniadakis 2007[99]	DOC: €5739 (95% CI €5037 to €6519) DOC + GEM: €7255 (95% CI €6565 to €7970)	DOC: 7.25 months (95% CI 6.29 to 8.23) DOC + GEM: 9.19 months (95% CI 8.98 to 10.51)	Incremental cost per LYS of DOC + GEM vs DOC: €9538	The data support that DOC + GEM represents a cost-effective treatment option in relation to DOC monotherapy for patients with NSCLC in the Greek setting
Neymark 2005[101]	CIS + PAX: €16,662 (95% CI €15,251 to €18,072) CIS + GEM: €13,944 (95% CI €12,829 to €15,060) GEM + PAX: €17,377 (95% CI €16,088 to €18,667)	**Mean MST in years:** CIS + PAX: 0.94 (95% CI 0.82 to 1.07) CIS + GEM: 0.98 (95% CI 0.86 to 1.11) GEM + PAX: 0.80 (95% CI 0.69 to 0.92)	CIS + GEM vs CIS + PAX: 72% of the replicates indicate CIS + GEM improves outcomes and reduces costs GEM + PAX vs CIS + PAX: 82% of the replicates indicate GEM + PAX reduces MST while increases the costs	The two CIS-based regimens are equivalent in terms of survival, but CIS + GEM may reduce costs by approximately €2000 per patient compared with PAX + CIS. GEM + PAX is a dominated option with higher costs and a reduction in MST compared with PAX + CIS

BEV, bevacizumab; ETOP, etoposide; MIC, mitomycin, ifosfamide and cisplatin; MVP, mitomycin, vinblastine and cisplatin; NS, not significant; OTR, overall tumour response; TTR, time to radiotherapy; VIN, vinblastine.

TABLE 47 Sensitivity analysis

Trial	Sensitivity analysis
Clegg 2001/2[39,93]	One-way sensitivity analysis was carried out across a range of variables including number of cycles (advice from clinical colleagues was that in routine care a more realistic scenario would be to assume 60% of patients would have only 1–2 cycles, while 40% would continue towards the recommended number of cycles: three for GEM, VNB and DOC regimens and four for PAX); number of administrations per cycle of VNB; best and worst cycles from trials; effect of discounts on BNF prices; and cost of newer antiemetic regimens. Mean survival estimates calculated from single trials by Berthelot 2000[121] and non-patient-based utility estimates were also examined. The cost of BSC, particularly the number of inpatient days (21 vs 19 days), was varied to reflect slight differences between sources. VNB, VNB + CIS and GEM retain their cost-effectiveness under a range of assumptions and may even be dominant under certain circumstances
Dooms 2006[94]	Extensive univariate sensitivity analysis has been performed using different cost ranges (from –50% to +50%) and cost items. Reducing the QALY gain increases the size of the ICER. The ICER is >€50,000 only when costs were increased by 50% and a lower QALY value (0.04) is used Changing the cost of drug administration has no real impact on the ICER, whereas varying the cost of the drug has the most significant impact
Klein 2009[95]	Several univariate sensitivity analyses were conducted on: number of PEM vials; non-squamous vs all NSCLC; responders receiving fifth and sixth chemotherapy cycle; unequal AE costs, equal mild side effects and discounting The tornado diagram described in the text shows that most reasonable changes in costs changed the ICER for PEM + CIS vs GEM + CIS by <10%
Lees 2002[97]	(1) Univariate sensitivity analyses were employed varying: costs of GEM acquisition and administration, outcomes measures using confidence limits and unit costs of chemotherapy administration. No significant changes in the ICERs were noted (2) Several univariate sensitivity analyses were performed using all non-chemotherapy costs (upper and lower bounds) resulting in no significant changes to the size of the ICER (3a/b) Costs/doses of all drugs in the group of novel therapies were varied; none of which changed the results significantly
Maniadakis 2007[99]	A PSA was carried out and shows that the probability of DOC + GEM being cost-effective in relation to DOC monotherapy is 91% at a threshold of €20,000, 97% at €35,000 and 98% at €50,000
Neymark 2005[101]	A univariate sensitivity analysis was conducted by varying hospital costs. The incremental costs between strategies did not vary

PSA, probabilistic sensitivity analysis.

cost-effective, as conventionally accepted, to being cost saving. The results of the sensitivity analyses only slightly change the results from the base-case analysis.

Dooms *et al.*[94] estimate an ICER of €13,836 per QALY in favour of GEM when compared with VNB + CIS; in the sensitivity analysis, the results are robust to credible changes in both costs and utilities.

Klein *et al.*[95] show that, as there are only slight differences in the total QALYs gained from each of the different regimens, the estimated ICERs exceed $100,000 per QALY gained when PEM + CIS is compared with (1) GEM + CIS and (2) PAX + CARB. For the non-squamous population only, ICERs exceed $150,000 per QALY gained. Reasonable changes introduced by undertaking sensitivity analyses do not change the base-case results by >10%.

Lees *et al.*[97] who do not use LYS or QALYs as a measure of health outcome, conclude that GEM alone or in combination with CIS is a cost-saving therapy when compared with BSC. The authors state that GEM + CIS is cost saving when compared with novel chemotherapies (PAX + CIS, PAX + CARB, DOC + CIS and VNB + CIS). No significant changes to the results were identified via sensitivity analysis.

Maniadakis *et al.*[99] found DOC + GEM to be a cost-effective regimen when compared with DOC alone at a threshold of €9538 per LYS with a 91% and 98% probability of being cost-effective when the threshold is set at €20,000 and €50,000, respectively.

Neymark *et al.*[101] did not find any differences in survival between patients receiving CIS + GEM and CIS + PAX, but concluded that the former may reduce costs by approximately €2000 per patient and stated that CIS + PAX is a dominant option when compared with GEM + PAX. The sensitivity analysis carried out on the base-case scenario did not lead to a change in the cost-effectiveness results.

Critique of published literature

This section provides a summary and a more detailed critique of the economic and clinical evidence used in the economic evaluation papers included in the review. The aim of the commentary set out in this section is to supplement the quality assessment exercise undertaken as part of the systematic review.

Clegg *et al.* 2001[39] and Clegg *et al.* 2002[93]

Methods of deriving the effectiveness data

In model 1, only two of the comparisons reviewed by Clegg *et al.*[39,93] compared chemotherapy with chemotherapy: GEM + CIS compared with GEM and VNB + CIS compared with VNB. In model 1, the pair-wise comparisons were based on the results of single trials only. In model 2, the authors make the assumption that the regimens have equal efficacy. In model 3, all relevant and available clinical effectiveness data are pooled using a mixed-treatment comparison approach as, at the time of writing, there was a lack of head-to-head evidence in this area.

Measurement and valuation of resource data

The main effectiveness measures used LYS and median number of chemotherapy cycles. Number of deaths or death rates at certain time points were not reported.

Measurement and valuation of health benefits (utilities)

Utilities have not been used, LYS are used as the main measure of health outcome.

Method of synthesising the costs and effects

Three different economic models were described in detail. Only the model incorporating pair-wise comparisons is able to comment on chemotherapy compared with chemotherapy and reports an ICER (cost per LYS); however, a limitation of this model is that each cost-effectiveness estimate was based on data from a single trial.

Analysis of uncertainty

Only univariate sensitivity analysis has been used to test the uncertainty related to use of data from different publications. Probabilistic sensitivity analysis (PSA) was not carried out.

Generalisability of the results

The authors have attempted to make the results of their economic models as generalisable to a UK population as possible. However, the authors conclude that comparisons among the chemotherapy drugs using the results of the CEA in model 3 should be viewed with caution because of the way the data were combined.

Dooms *et al.* 2006[94]

Methods of deriving the effectiveness data

Data from a Phase III RCT comparing GEM with VNB + CIS were used. Reliance on a single trial as a source of clinical effectiveness data may be seen as a limitation of the economic evaluation. The main clinical effectiveness measure used was OS. The author states that as small differences in OS were identified

between regimens and bigger differences in QoL and clinical benefit were also identified, a CUA was performed using QALYs.

Measurement and valuation of resource data
Resource-cost data were calculated from a RCT. The RCT used for this economic evaluation is not fully reported in the economic paper, but is fully referenced. Some cost items were considered to be equivalent across the two interventions and were not included in the economic evaluation.

Measurement and valuation of health benefits (utilities)
Quality-adjusted life-years and LYS were used in the economic evaluation. The method used to convert a global visual analogue score into a utility score is not fully described. The authors acknowledge that they could be criticised for this approach.

Method of synthesising the costs and effects
A CUA has been used to synthesise both cost and health outcomes in the form of an ICER.

Analysis of uncertainty
The authors have explored the effect of varying costs and utilities on the size of the incremental cost–utility ratio. PSA was not carried out.

Generalisability of the results
The setting for the economic evaluation was Belgium which means that the results are unlikely to be generalisable to a UK setting without an additional description of Belgian clinical practice and estimation of costs. As GEM monotherapy and VNB + CIS combination therapy are not routinely used as standard chemotherapy regimens in the UK, it is unlikely that the results will help health professionals make decisions that are relevant to a UK population.

Klein *et al.* 2009[95]

Methods of deriving the effectiveness data
Efficacy data were obtained from a head-to-head trial comparing PEM + CIS and GEM + CIS regimens; for comparisons between PEM + CIS and PAX + CARB and with PAX + CARB + bevacizumab (BEV) regimens, data were derived from the results of a mixed-treatment comparison exercise. The calculation of the transition probabilities in the semi-Markov model is not fully explained.

Measurement and valuation of resource data
Costs are taken from the Medicare reimbursement rates.

Measurement and valuation of health benefits (utilities)
Differential survival and response rates for PAX + CARB and PAX + CARB + BEV were taken from a mixed-treatment comparison model; very little data on this model were provided and the reference cited was from a conference abstract. QALYs were calculated using the utility values estimated by Nafees *et al.*[116] which take account of toxicities and response rates. However, there is insufficient information in the paper to explain how these utility values were derived which means it is not possible to assess the robustness of these calculations. As the values are central to the author's conclusions, the inability to assess the calculations limits the usefulness of their findings.

Method of synthesising the costs and effects
The author has used a semi-Markov model with an initial simple decision tree covering a 6-month period followed by three 6-month cycles. The base-case ICER was estimated for patients with non-squamous NSCLC only, a second analysis was presented which estimates ICERs for all patients.

Analysis of uncertainty
Several univariate sensitivity analyses have been performed by the authors and were presented as a tornado diagram showing that changes in costs do not lead to variations in the cost-effectiveness results by > 10%. A PSA has not been employed.

Generalisability of the results
The setting of this economic evaluation is the US Medicare system which differs to the NHS not only in the finance and provision of chemotherapy regimens but also in the costs of administration. Two of the treatment options considered in the economic evaluation are of interest to UK decision-makers (PEM + CIS and GEM + CIS) and it is particularly useful that the authors provide ICERs for the population with non-squamous disease as well as the overall population (but these are based on QALYs, where we are unsure how the authors have incorporated utility).

Lees *et al.* 2002[97]

Methods of deriving the effectiveness data
The authors used several head-to-head trials to inform the clinical base of the economic model. However, the authors did not state reasons for selecting these particular trials. Outcome measures used in the selected trials included OS, PFS and response rates. Comparison of GEM + CIS with novel chemotherapy was based on clinical data derived from two large trials (one of which was an interim analysis).

Measurement and valuation of resource data
Quantities of health-care resource use have been derived from the RCTs described. Costs were derived from NHS reference costs.

Measurement and valuation of health benefits (utilities)
No utilities have been used in this economic evaluation.

Method of synthesising the costs and effects
The author has used ICERs in terms of cost per progression-free life-year or incremental costs only; the ICER, therefore, does not reflect QoL lost related to the toxicity of treatment.

Analysis of uncertainty
Several univariate sensitivity analyses were undertaken using upper and lower bounds of the cost parameters. No sensitivity or scenario analysis was undertaken on efficacy parameters.

Generalisability of the results
The economic evaluations use UK costs and as the RCTs are multicentre trials, they appear to make the economic results generalisable to the UK setting. The comparison of GEM + CIS with novel chemotherapy is the most interesting to UK decision-makers. However, close scrutiny of the assumptions used in the base-case scenarios is merited; for example, PAX is given as a 24-hour i.v. therapy which is rarely the case in the UK and cost of median compared with mean number of treatment cycles influences the size of the ICER.

Maniadakis *et al.* 2007[99]

Methods of deriving the effectiveness data
This economic evaluation is conducted alongside a multicentre Phase III RCT in Greece. TTP, OS, RRs and number of deaths were collected from the trial but the author stated that only median OS was to be used in the economic evaluation.

Measurement and valuation of resource data
Resource-use data were collected from the key RCT. The economic evaluation assumes no drug wastage. A detailed description of unit cost data is presented in the paper; data were taken from Greek national

sources and the database of the University General Hospital of Heraklion. For example, the cost of chemotherapy was calculated by multiplying the exact dose given with cost per mg.

Measurement and valuation of health benefits (utilities)
No utilities have been used in the economic evaluation, only LYS have been estimated.

Method of synthesising the costs and effects
Incremental cost per LYS was used as the cost-effectiveness ratio of interest. No toxicity or QoL results were incorporated into the economic evaluation.

Analysis of uncertainty
A PSA was performed to quantify data uncertainty and demonstrated that the DOC + GEM combination was very likely to be cost-effective compared with DOC monotherapy.

Generalisability of the results
The cost and benefit data used in the study was specific to the Greek NHS. As GEM and DOC are now off patent and DOC + GEM is not used as a standard chemotherapy regimen in the UK, it is unlikely that the results will help health professionals make decisions that are relevant to a UK population.

Neymark *et al.* 2005[101]

Methods of deriving the effectiveness data
Efficacy data were derived from a prospective RCT; the economic evaluation was conducted alongside the RCT. Only data on survival were used in the economic evaluation.

Measurement and valuation of resource data
Prospective collection of data on the use of medical resources was integrated in the case report forms of the trial. Where data were not sufficiently precise to allow measurement, assumptions were made using set protocols and published literature. Unit prices of resources used in the trial are detailed in the paper; resource utilisation, mean quantities and proportions of patients are also described.

Measurement and valuation of health benefits (utilities)
No utilities have been used. The objective of the economic evaluation was to estimate an average cost per patient related to survival. There is no discussion of toxicity or QoL in the paper.

Method of synthesising the costs and effects
Differences between the mean cost per patient in each regimen were calculated using bootstrapping techniques with 5000 iterations. No ICERs were presented.

Analysis of uncertainty
The limited sensitivity analysis conducted by the authors was focused on the impact of varying hospital costs on total costs.

Generalisability of the results
Study results are interpretable to decision-makers in a hospital setting in the Netherlands. However, owing to the lack of health outcome measurements and failure to report ICERs, these results are of limited validity to decision-makers in the UK NHS.

Are the results of the reports included in the systematic review relevant to UK decision-makers?
As shown in *Table 48*, the results of the seven papers[39,93–95,97,99,101] considered in the systematic review of first-line chemotherapy for patients with NSCLC are unlikely to aid decision-makers in the UK. First, the comparisons that have been the focus of the papers are not all standard NHS treatments and, second, only two of the reports present their findings in terms of cost per QALY gained.

TABLE 48 Are published NSCLC trials relevant to NHS decision-makers?

Studies described in the systematic review	UK setting?	Relevant comparisons?	ICER (cost per QALY) estimated?	Relevance to NHS decision-making?
Clegg 2001/2[39,93]	Yes	None	No	Limited
Dooms 2006[94]	No	None	Yes	Poor
Klein 2009[95]	No	PEM + CIS vs: • GEM + CIS • PAC + CARB • PAC + CARB + BEV	Yes	Limited
Lees 2002[97]	Yes	GEM + CIS vs: • PAC + CIS • PAC + CARB • DOC + CIS • VIN + CIS	No	Limited
Maniadakis 2007[99]	No	None	No	Poor
Neymark 2005[101]	No	PAC + CIS vs GEM + CIS	No	Limited

VIN, vinblastine.

Other sources of economic evidence

In order to inform the debate and make use of relevant clinical effectiveness and cost-effectiveness data we have summarised the findings from two recent Evidence Review Group (ERG) reports[122,123] on first-line treatments for patients with NSCLC. The ERG reports inform the NICE STA process and are written prior to the first Appraisal Committee (AC) meeting. Neither of these reports were identified by the literature searches, as they are not published in a peer-reviewed journal. The ERG reports[122,123] are focused on two subgroups of patients with NSCLC: (1) patients with non-squamous disease and (2) patients who are EGFR+.

Patients with non-squamous disease

The manufacturer's submission (MS) for this STA[122] included a de novo economic evaluation comparing PEM + CIS with GEM + CIS in patients with non-squamous disease using clinical effectiveness data from the trial by Scagliotti *et al.*[61]

Patients who are epidermal growth factor receptor mutation positive

The MS for the second STA[123] included a de novo economic evaluation comparing GEF with PAX + CARB in patients who are EGFR+ using clinical effectiveness data from the IPASS.[15]

Adherence to the National Institute for Health and Care Excellence reference case and critical appraisal of economic evaluations

Tables 49 and *50* provide the ERG summary/critique of the de novo economic evaluations performed by the manufacturers and show whether or not the approach adopted by the manufacturer adheres to the reference case outlined by NICE.

In the case of PEM, according to the ERG,[122] the manufacturer's economic evaluation did not fully adhere to the NICE reference case, in particular with regards to the inclusion of all relevant comparators. The ERG also found that the manufacturer's economic evaluation had quality issues identified by the Drummond and Jefferson checklist,[106] again, owing to the omission of key comparators, but also because of problems with valuing outcomes.

TABLE 49 Critical appraisals by the ERG

Item	ERG critique (PEM)[122]	ERG critique (GEF)[124]
Was a well-defined question posed in answerable form?	The manufacturer did not fully address the decision problem (VNB and PAX not included)	The manufacturer only partially answered the decision problem set by NICE as (1) DOC and (2) PEM were not included
Comprehensive description of competing alternatives?	The manufacturer described the chosen comparators adequately	The manufacturer described the chosen comparators adequately
Was the effectiveness of the programme or services established?	Evidence from the JMDB trial demonstrated the clinical non-inferiority of PEM + CIS compared with GEM + CIS. The trial was not powered to detect subgroup analyses, which the manufacturer relies on heavily in the model. Also, for the comparisons with DOC + CIS and GEM + CARB, the manufacturer conducted indirect analysis; however, the methodology employed to achieve this was flawed	It is unclear to what extent treatment effectiveness is established for a UK population primarily because patients in the IPASS are younger, predominantly female, oriental, have adenocarcinoma histology and include patients whose PS = 2; these patients do not represent patients eligible for treatment with GEF in England and Wales. The ERG has also expressed its concern regarding the methods used in the meta-analysis and in the mixed-treatment comparison which supply the main sources of clinical effectiveness evidence; in particular, the ERG questions the validity of assuming differential efficacy rates for the four doublet chemotherapy regimens considered in the economic evaluation
All important/relevant costs/consequences identified?	Key costs and consequences were identified	The key costs and outcomes were identified. ERG proposed not to include g-CSF costs as this is not used in clinical practice in NHS
Were costs/consequences measured accurately in appropriate physical units?	For example, the BSA value used to calculate chemotherapy costs does not represent NSCLC patients in the UK	The BSA value used to calculate chemotherapy costs does not represent patients with NSCLC in the UK; cost per cycle of chemotherapy and second-line chemotherapy were estimated incorrectly
Costs/consequences valued credibly?	Modelled OS and PFS were inaccurate and overestimated for some trial values	OS was not adequately modelled; poor correspondence between parametric survival models and source data
Were costs/consequences adjusted for differential timing?	The method of discounting was appropriate	Costs and outcomes were discounted after 1 year; method of discounting did not conform to UK convention of discounting annually after year 1
Was an incremental analysis of costs and consequences of alternatives performed?	ICERs (cost per QALY gained and cost per LYG) were presented for the base-case population and subgroups	Pair-wise incremental results presented for the base-case target population and subgroups (adeno vs non-adeno; females vs males; never smokers vs ever smokers)
Was allowance made for uncertainty in the estimates of costs and consequences?	Univariate SA and PSA were undertaken by the manufacturer	PSA and univariate SA and scenario analysis were also undertaken by the manufacturer but only limited results of the one-way SA undertaken were presented in the MS
Did the presentation and discussion of study results include all issues?	Not all comparators have been included	The results are presented and discussed in detail. Resources and infrastructure required to implement a universal EGFR mutation test for eligible patients is not fully discussed in the MS

BSA, body surface area; g-CSF, granulocyte-colony stimulating factor; SA, sensitivity analysis.

TABLE 50 The NICE reference case checklist

Attribute	Does the de novo economic evaluation match the reference case? (PEM)[122]	Does the de novo economic evaluation match the reference case? (GEF)[123]
Comparator(s) (therapies routinely used in the NHS)	Therapies routinely used in the NHS include GEM, VNB, DOC and PAX with a PLAT. VNB and PAX not included	Partially. Economic evaluation does not include DOC or PEM as comparators; both these comparators are routinely used in the NHS
Perspective costs (NHS/PSS)	The economic evaluation is carried out from the perspective of the NHS. No social costs are described in the MS	The economic evaluation is carried out from the perspective of the NHS. No social costs are described in the MS
Perspective benefits	Health effects to the individual are captured via QALYs	Health effects to the individual are captured via QALYs
Economic evaluation (CEA)	CEA	CEA
Time horizon (capture differences in costs/outcomes)	The time horizon chosen was a lifetime horizon (6 years). This appears appropriate	The time horizon chosen was a lifetime horizon, which for this patient group was believed to be 5 years. This appears to be appropriate
Synthesis of evidence on outcomes (systematic review)	All outcome data are derived from RCTs. Indirect methodology was utilised, although this was *not* applied correctly	All survival data are derived (and where appropriate extrapolated) from a mix of clinical data sources: the IPASS RCT, meta-analysis (IPASS and NEJGSG) and mixed-treatment comparison; the meta-analysis and mixed-treatment comparison were based on systematic reviews of the literature
Outcome measure (QALYs)	QALYs were used, which is appropriate	QALYs were used which is appropriate
Health states for QALY (standardised and validated instrument)	QoL data were not available from any of the trials, therefore a published QoL study[116] was utilised. This is *not* ideal, but the utility values appear to be reasonable	In the IPASS QoL was not measured in terms of utility. After a systematic review conducted by the manufacturer did not identify any relevant utility values for use in the economic evaluation, the utility values from Nafees 2008[116] was used
Benefit valuation	The QoL study[116] utilised SG interview techniques, which is acceptable	The main QoL Nafees *et al*.[116] study utilised standard gamble interview techniques, which is acceptable
Source of preference data for valuation of changes in HRQoL (TTO or SG)	The QoL study[116] was based on responses from 100 members of the general public. It is not clear how representative this sample is	Main QoL study by Nafees *et al*.[116] was based on responses from 105 members of the general public. Unclear how representative this sample is of the UK adult population. Furthermore, the QoL study was not specifically designed to capture the QoL of patients requiring first-line treatment
Discount rate (3.5%)	Benefits and costs, where appropriate, have been discounted using the 3.5% rate	Benefits and costs have been discounted using a rate of 3.5%
Equity (QALYs have equal weight)	All QALYs estimated by the economic model have the same weight	All QALYs estimated by the economic model have the same weight
Sensitivity analysis (PSA)	A PSA was conducted by the manufacturer	A PSA was conducted by the manufacturer

NEJGSG, North East Japan Gefitinib Study Group; PSS, Personal Social Services; SG, standard gamble; TTO, time trade-off.

In the case of GEF, according to the ERG,[123] the manufacturer had attempted to adhere to the NICE reference case. However, as DOC and PEM are not included as comparators in the economic evaluation performed by the manufacturer, not all therapies routinely used in the NHS were considered. Furthermore, the ERG believed that the source of utility values used in the economic model might not be appropriate to the decision problem. The ERG reported that the manufacturer's submitted model failed on a number of issues including the exclusion of valid comparators and the incorrect identification and measurement of key costs and benefits. The ERG also highlighted that the manufacturer employed differential efficacy rates for the four chemotherapy regimens considered in the economic evaluation whereas the results of the manufacturer's own mixed-treatment comparison demonstrate equivalent efficacy rates for the same four chemotherapy regimens. Ultimately, the ERG questioned to what extent the clinical effectiveness of GEF is established for use in clinical practice in England and Wales.

The ERG reports are one of multiple sources of evidence for use in the first AC meeting. The recommendations set out in the appraisal consultation document and in the final appraisal document are not solely based on the ERG report. After the first AC meeting, second and/or third AC meetings may also take place to discuss any unresolved issues about the clinical effectiveness and cost-effectiveness evidence presented. The AC considered PEM + CIS at two AC meetings and GEF at three AC meetings. The final ICER estimates and conclusions of the AC for PEM + CIS and GEF are summarised in *Table 51* and are described in the Final Appraisal Determination[13,16] issued by NICE. For the non-squamous population, PEM + CIS appears to be cost-effective compared with GEM + CIS. For the EGFR+ population, GEF appears to be cost-effective compared with PAX + CARB when the manufacturer provides GEF at a reduced price.

Discussion and conclusions of economic evidence available

It is clear from the preceding sections that, although there exists published cost-effectiveness evidence comparing different first-line chemotherapy regimens for patients with NSCLC, very few studies are directly helpful to decision-makers in the NHS because the studies are not UK focused and/or they do not estimate ICERs in terms of cost per QALY gained.

The newer drugs that are now available to treat patients with NSCLC are not suitable for use in the overall NSCLC population and it is likely that the targeting of drugs to specific groups of patients will continue to play a role in the future development of drugs in this field. In contrast to the older drugs, newer drugs are subject to appraisal by NICE and the cost-effectiveness evidence submitted by manufacturers in support of these new drugs is more relevant to the needs of NHS decision-makers than ever before. However, there is a paucity of economic evaluations considering the use of the newer drugs for patients with NSCLC.

TABLE 51 Cost per QALY ICERs of first-line chemotherapy considered in the STA process by NICE

Interventions	ERG (ICER estimate)	Manufacturer (ICER estimate)	NICE conclusions
PEM + CIS vs GEM + CIS[13]	< £30,000 for patients with non-squamous disease; < £25,000 for patients with adenocarcinoma/large cell carcinoma	< £30,000 for patients with non-squamous disease; < £25,000 for patients with adenocarcinoma/large cell carcinoma	PEM + CIS is recommended as an option for the first-line treatment of patients with adenocarcinoma or large cell carcinoma
GEF vs PAX + CARB[16]	£23,000 to £64,000	£19,000 to £23,000	GEF is recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if: • they test positive for EGFR-TK mutation; and • the manufacturer provides GEF at the fixed price agreed under the Patient Access Scheme

In summary, the conclusions of our systematic review echo the conclusions of the review by Carlson *et al.*[125] that was published in 2008. Carlson *et al.*[125] conclude that: 'The results...reflect the large number of treatment strategies available in the treatment of NSCLC... given the absence of trials on newer therapeutics and the lack of CUAs, additional trials appear to be warranted, especially those that incorporate QoL considerations in the comparison of treatment strategies...'.[125]

Independent economic assessment: methods

Assessment perspective

Costs and outcomes are assessed from the perspective of the UK NHS and Personal Social Services. Wider indirect costs and benefits (e.g. loss of productivity, value of informal care and impact on utility of patient's family) are not considered.

Relevant patient populations

Three distinct populations are modelled as follows:

1. chemotherapy-naive adult patients with locally advanced or metastatic NSCLC, which is *not* of predominantly non-squamous histology (referred to as 'squamous disease population')
2. chemotherapy-naive adult patients with locally advanced or metastatic NSCLC of predominantly non-squamous histology whose tumour(s) have not been shown to be EGFR M+ for activating mutations (referred to as 'non-squamous disease population')
3. chemotherapy-naive adult patients with locally advanced or metastatic NSCLC of predominantly non-squamous histology whose tumour(s) have been shown to be EGFR positive for activating mutations (referred to as 'EGFR M+ population').

Population (1) may only be treated with third-generation doublet chemotherapy. Population (2) may receive PEM + PLAT chemotherapy or a third-generation doublet chemotherapy. Population (3) has potentially the widest range of treatment options including those targeted for EGFR-activating mutations such as GEF, but no evidence is available for the efficacy of PEM + PLAT chemotherapy in this population subgroup.

Treatment options to be evaluated

A total of 12 first-line chemotherapy regimens are incorporated into the model (five primary licensed products used in combination with either CIS or CARB, PEM in combination with CIS, and GEF monotherapy). Details of these regimens are shown in *Table 52* (together with two agents available for second-line chemotherapy), and correspond to the information contained in the Summary of Product Characteristics for each product. Information on the likely setting for treatment administration was provided by clinical advisors. CARB-based i.v. combination therapy is always delivered in a day-case unit. DOC is also administered in a day-case unit irrespective of the choice of PLAT compound. For other CIS-based combination regimens, there is variation in practice concerning the proportions of patients treated as inpatients or day cases.

Carboplatin has no licensed indication for use in combination therapy for advanced NSCLC, but is widely used as a less toxic alternative to CIS.

In the base-case analysis it is assumed that equal numbers of patients suitable for second-line chemotherapy receive DOC monotherapy and 50% receive ERL. However, patients receiving DOC as first-line chemotherapy will not be re-exposed to it, and therefore may only receive ERL in second-line treatment.

Although PEM is licensed as monotherapy for second-line chemotherapy, it has not been considered alongside DOC and ERL as an alternative i.v. treatment since it is substantially more expensive than DOC

TABLE 52 First- and second-line chemotherapy regimens modelled

Regimen	Chemotherapy	Population	Cycles	Doses per cycle	Dose given (mg/m²)	Comedications	Setting
First line							
1 A/B	DOC i.v.	Any NSCLC	4 × 21 days	1	75	Dexamethasone	Day case
2 A/B	GEM i.v.	Any NSCLC	4 × 21 days	2	1250	No	A: Inpatient or day case B: Day case
3 A/B	PAX i.v.	Any NSCLC	4 × 21 days	1	175	Dexamethasone, chlorphenamine, ranitidine	A: Inpatient or day case B: Day case
4 A/B	VNB i.v.	Any NSCLC	4 × 21 days	1	25 first cycle, 30 thereafter	No	A: Inpatient or day case B: Day case
5 A/B	VNB oral	Any NSCLC	4 × 21 days	1	60 first cycle, 80 thereafter	No	A: Inpatient or day case B: Day case
6 A	PEM i.v.	Non-squamous	4 × 21 days	1	500	Dexamethasone, hydroxocobalamin, folic acid	Inpatient or day case
7	GEF oral	EGFR M+	To progression	Daily	250-mg tablet	No	Outpatient
Second line							
8	DOC i.v. monotherapy	Not previously treated with DOC	4 × 21 days	1	75	Dexamethasone	Day case
9	ERL oral	Any NSCLC	To progression	Daily	150-mg tablet	No	Outpatient

A, combined with CIS 75 mg/m² once per cycle; B, combined with CARB AUC 5 once per cycle.

and is not recommended by NICE for use in the NHS. This limitation is likely to have a minimal effect on the cost-effectiveness of first-line regimens.

Model design

The decision model (*Figure 25*) is conceptually straightforward, involving three health states prior to death, and up to two lines of chemotherapy. Chemotherapy is treated as an extended event, normally restricted to a maximum of 12 weeks in duration (four cycles each of 3 weeks). The only exception is for orally administered treatments given continuously until the disease progresses (i.e. GEF and ERL) where treatment is assumed to be coterminous with the duration of the PFS state.

Disease progression after either first- or second-line therapy is also treated as an event, resulting in one of three possible transitions: to further active therapy (only after first-line chemotherapy), to supportive care only or to death.

The model is implemented as a Microsoft Excel workbook (Microsoft Corporation, Redmond, WA, USA), using macro programming to perform PSA to assess the relative probabilities of cost-effectiveness between the available first-line treatments.

Ideally, the model should be driven by evidence from clinical trials relating to each of the model's health states: the duration of PFS until first confirmed disease progression, the duration of PFS following second-line treatment, and the duration of postprogression survival (PPS) receiving only BSC. Unfortunately, the only outcomes routinely reported for clinical trials are PFS (first-line chemotherapy) and OS. Thus, the model can only be populated indirectly, by inferring the likely experience of patients in the intermediate

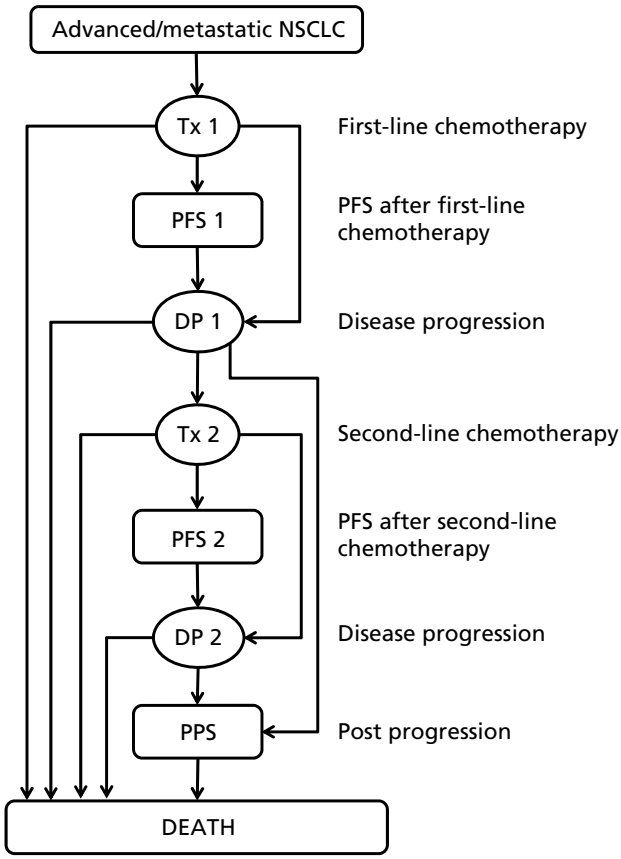

FIGURE 25 Conceptual model of NSCLC decision model, indicating health states (rectangles), events/procedures (ovals) and transitions (arrows). DP, disease progression; PPS, postprogression survival; Tx 1, first-line chemotherapy treatment; Tx 2, second-line chemotherapy treatment.

states. This leads to potentially serious difficulties and inconsistencies in model implementation. In particular, the normal practice of treating PFS and OS as independent variables is naive, as PFS is a major component of OS. Not recognising this easily leads to situations where deriving an estimate for PPS by subtracting estimated PFS from estimated OS leads to erroneous negative values at some point during the simulation period. The modeller has to exercise great care at every stage of model development, calibration and use to guard against producing nonsensical results.

Synthesis of survival evidence: squamous and non-squamous disease

Effectiveness evidence from clinical trials identified as relevant to each population were synthesised in two stages: data from individual trial arms are pooled to produce a risk profile representative of each available treatment option, then a mixed-treatment comparison at a common time point was employed to estimate HRs to allow these risk profiles to be mutually calibrated while preserving randomisation within each trial.

Agent-specific outcome profiles

Kaplan–Meier estimates for OS and PFS/TTP for each regimen were compared across all trials and were pooled in order to obtain a standard cumulative hazard profile, which reflects the temporal changes in hazard typical of each chemotherapy agent. This involved extracting monthly survival estimates for 0–24 months from trial reports and then pooling these trends, weighting each data point by the number of patients in each included trial arm. The resulting survival estimates were then converted to cumulative hazards. The resulting hazard profile was then standardised to match the pooled value of a reference chemotherapy agent (PAX) at 12 months. These profiles do not distinguish between CIS and CARB doublets, which are assumed to be equivalent in terms of clinical effectiveness.

Table 53 details the PFS and OS profiles for months 0–24. In each case a piecewise profile model was fitted by least-squares regression using linear or quadratic segment functions, as described mathematically in *Table 54*. Constrained regression analysis (using SPSS 18; SPSS Inc., Chicago, IL, USA) was employed to generate parameter estimates for each model.

The cumulative hazard profile models are illustrated in *Figures 26–29* (see *Figures 26* and *28* for PFS and *Figures 27* and *29* for OS). These suggest that the third-generation agents generate outcomes in quite similar ways, though exhibiting more divergence in the second year of survival when some treatments show an apparent moderation of long-term risks.

When these profiles are examined in the form of traditional survival curves, differences in the short term are more easily seen, especially for the PFS models.

Hazard ratios

Derivation and application of hazard ratios

Hazard ratios for OS and PFS/TTP were obtained from a network meta-analysis of relevant trials based on determining the HR of each first-line regimen relative to a PAX doublet regimen. *Table 55* shows the values obtained for use as model parameters; full details of the mixed-treatment comparison are shown in *Chapter 3, Population 1: non-small cell lung cancer patients with squamous disease* and *Chapter 3, Population 2: non-small cell lung cancer patients with non-squamous disease*. HRs only differed significantly from PAX for OS in the case of PEM.

These HRs were then applied to adjust the standardised cumulative hazard profile of each regimen to obtain a final characterisation of treatment effectiveness of each regimen for use in the decision model.

Uncertainty in hazard ratios

Ideally, the model would have been constructed using PFS and PPS as the primary outcome measures, with OS used as a confirmation of model reliability. Unfortunately, PPS is not reported in clinical trials and the model was constructed to reflect the PFS and OS data available. This presents a difficulty for projective

TABLE 53 Standardised treatment-specific cumulative hazard profiles obtained by pooling treatment arms from RCTs (PAX used as referent to standardise profiles at 12 months)

	Treatment									
	PAX		DOC		GEM		VNB		PEM	
Month	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.103	0.045	0.096	0.055	0.076	0.038	0.087	0.042	0.057	0.035
2	0.373	0.098	0.379	0.108	0.255	0.094	0.306	0.080	0.209	0.079
3	0.530	0.172	0.506	0.172	0.392	0.157	0.525	0.144	0.314	0.139
4	0.670	0.247	0.641	0.235	0.542	0.218	0.720	0.212	0.452	0.207
5	0.936	0.328	0.901	0.316	0.771	0.311	0.847	0.287	0.687	0.267
6	1.117	0.419	1.092	0.388	1.002	0.401	1.142	0.370	0.923	0.394
7	1.377	0.523	1.257	0.491	1.277	0.504	1.347	0.455	1.287	0.507
8	1.615	0.615	1.542	0.594	1.527	0.585	1.449	0.573	1.589	0.594
9	1.792	0.703	1.811	0.693	1.791	0.676	1.800	0.659	1.810	0.687
10	2.003	0.804	1.913	0.799	1.992	0.767	2.019	0.762	1.991	0.801
11	2.214	0.891	2.214	0.883	2.196	0.879	2.169	0.866	2.195	0.888
12	2.379	0.983	2.379	0.983	2.379	0.983	2.379	0.983	2.379	0.983
13	2.527	1.096	2.556	1.114	2.548	1.083	2.450	1.064	2.516	1.071
14	2.638	1.193	2.671	1.195	2.705	1.203	2.678	1.182	2.876	1.161
15	2.723	1.278	2.817	1.236	2.802	1.288	2.768	1.296	2.876	1.295
16	2.856	1.349	3.135	1.320	2.970	1.370	2.944	1.398	2.968	1.413
17	2.979	1.410	3.445	1.374	3.090	1.443	2.993	1.490	3.071	1.460
18	3.110	1.493	3.605	1.457	3.180	1.515	3.561	1.601	3.071	1.538
19	3.266	1.566	3.605	1.492	3.289	1.606	3.637	1.681	3.247	1.656
20	3.389	1.661	3.994	1.567	3.372	1.685	3.729	1.785	3.247	1.717
21	3.389	1.754	4.218	1.627	3.413	1.756	3.976	1.876	3.247	1.810
22	3. 495	1.858	4.307	1.681	3.587	1.887	3.976	1.941	3.389	1.841
23	3.701	1.931	4.307	1.800	3.701	1.988	4.570	2.043	3.389	1.944
24	3.752	1.959	4.307	1.845	3.818	2.077	4.570	2.122	3.389	1.996
Sources	47, 43, 46, 56, 57, 60	43, 46–48, 51, 56, 57, 60	47, 59	44, 47, 53, 65	43, 46, 47, 54, 56, 57, 60, 61	43, 46, 47, 50, 54–58, 60, 61	43, 54 58	43, 44, 48, 50, 51, 53, 54, 57, 58	61	61

DOC, DOC + PLAT; GEF, GEF in EGFR+ population; GEM, GEM + PLAT; PAX, PAX + PLAT; PEM, PEM + CIS in non-squamous population; TX, first-line treatment; VNB, VNB + PLAT.

TABLE 54 Standardised treatment-specific cumulative hazard profile model equations (PAX used as referent to standardise profiles at 12 months)

Regimen	PFS profile cumulative hazard model	OS profile cumulative hazard model
PAX + PLAT	$H(t) = 0.19821 \times t$ *[t < 12.40 months]* $H(t) = 2.457 + 0.11459 \times (t - 12.40)$ *[t ≥ 12.40 months]*	$H(t) = 0.04465 \times t$ *[t < 1.53 months]* $H(t) = 0.087 + 0.08739 \times (t - 1.53)$ *[t ≥ 1.53 months]*
DOC + PLAT	$H(t) = 0.19821 \times t$ *[t in months]*	$H(t) = 0.06012 \times t$ *[t < 5.18 months]* $H(t) = 0.311 + 0.09852 \times (t - 5.18)$ *[5.18 ≤ t < 14.00 months]* $H(t) = 1.180 + 0.06557 \times (t - 14.00)$ *[t ≥ 14.00 months]*
GEM + PLAT	$H(t) = 0.12583 \times t$ *[t < 3.19 months]* $H(t) = 0.401 + 0.22441 \times (t - 3.19)$ *[3.19 ≤ t < 13.14 months]* $H(t) = 2.635 + 0.10776 \times (t - 13.14)$ *[t ≥ 13.14 months]*	$H(t) = 0.04544 \times t$ *[t < 2.55 months]* $H(t) = 0.116 + 0.09181 \times (t - 2.55)$ *[t ≥ 2.55 months]*
VNB + PLAT	$H(t) = 0.19821 \times t$ *[t < 12.00 months]* $H(t) = 2.379 + 0.16717 \times (t - 12.00)$ *[t ≥ 12.00 months]*	$H(t) = 0.04946 \times t$ *[t < 4.07 months]* $H(t) = 0.201 + 0.09862 \times (t - 4.07)$ *[t ≥ 4.07 months]*
PEM + CIS	$H(t) = 0.04051 \times t + 0.01982 \times t^2$ *[t < 7.94 months]* $H(t) = 1.573 + 0.19870 \times (t - 7.94)$ *[7.94 ≤ t < 14.62 months]* $H(t) = 2.899 + 0.06943 \times (t - 14.62)$ *[t ≥ 14.62 months]*	$H(t) = 0.02503 \times t + 0.00650 \times t^2$ *[t < 7.00 months]* $H(t) = 0.494 + 0.09793 \times (t - 7.00)$ *[7.00 ≤ t < 17.68 months]* $H(t) = 1.540 + 0.07417 \times (t - 17.68)$ *[t ≥ 17.68 months]*

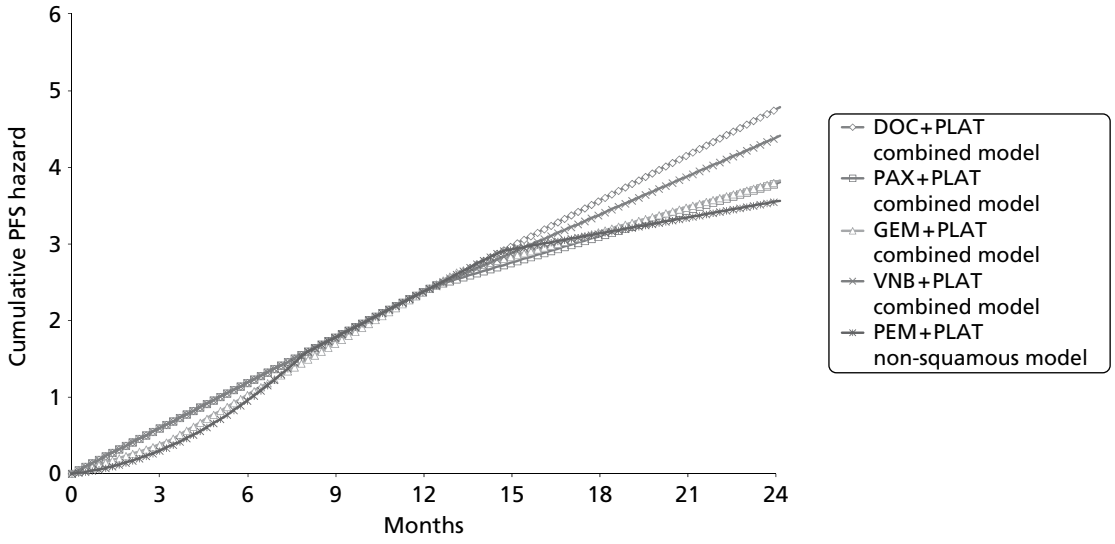

FIGURE 26 Progression-free survival profile cumulative hazard models, standardised to PAX at 12 months.

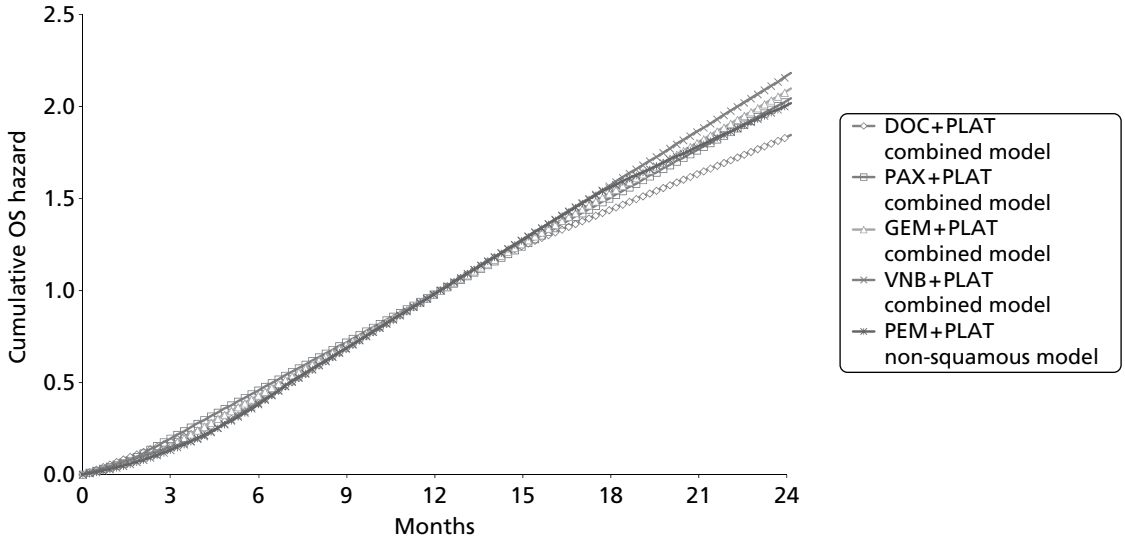

FIGURE 27 Overall survival profile cumulative hazard models, standardised to PAX at 12 months.

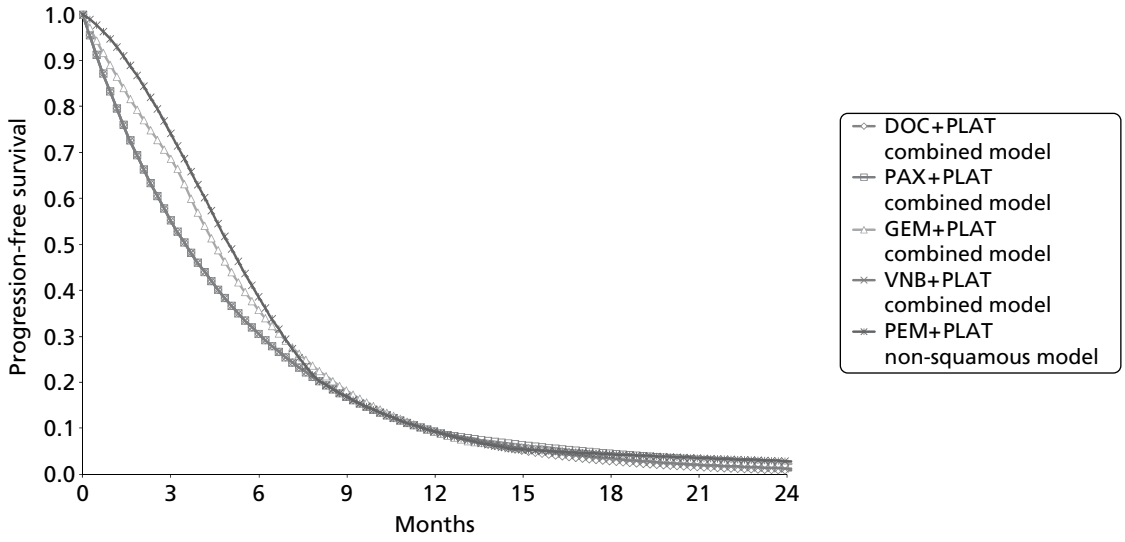

FIGURE 28 Progression-free survival profile models, standardised to PAX at 12 months.

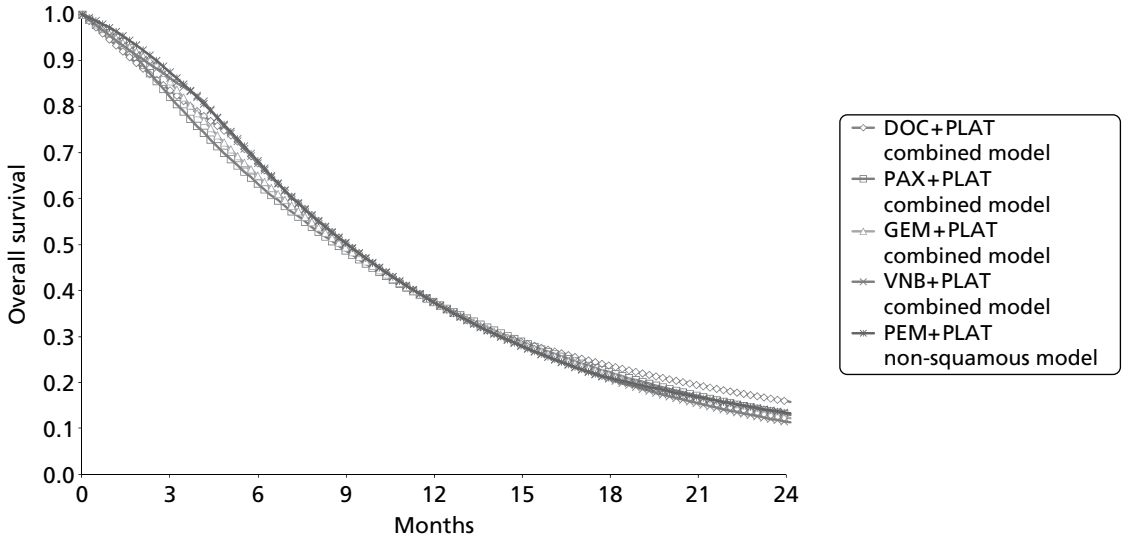

FIGURE 29 Overall survival profile models, standardised to PAX at 12 months.

TABLE 55 Hazard ratios relative to PAX for model populations estimated by mixed-treatment comparison

Regimen	HR	LCL	UCL	SE(ln[HR])	*p*-value
Squamous disease	PFS				
PAX	1.000	–	–	–	–
DOC	0.966	0.785	1.168	0.101	0.365
VNB	0.923	0.823	1.031	0.058	0.082
GEM	0.971	0.829	1.134	0.080	0.355
Squamous disease	OS				
PAX	1.000	–	–	–	–
DOC	0.942	0.805	1.106	0.081	0.232
VNB	0.953	0.870	1.045	0.047	0.154
GEM	1.040	0.928	1.168	0.059	0.745
Non-squamous disease	PFS				
PAX	1.000	–	–	–	–
DOC	0.961	0.787	1.171	0.102	0.363
VNB	0.922	0.823	1.033	0.058	0.080
GEM	0.971	0.832	1.134	0.079	0.356
PEM	0.831	0.653	1.049	0.121	0.063
Non-squamous disease	OS				
PAX	1.000	–	–	–	–
DOC	0.942	0.803	1.106	0.082	0.230
VNB	0.954	0.871	1.045	0.046	0.155
GEM	1.040	0.931	1.168	0.058	0.748
PEM	0.770	0.636	0.941	0.100	0.005

LCL, lower 95% confidence limit for HR; UCL, upper 95% confidence limit for HR; SE(ln[HR]), standard error of the natural logarithm of the estimated HR.

p-value is significant at $p < 0.05$.

modelling, and also in the representation of parameter uncertainty when carrying out PSA. Patient numbers in PPS are usually estimated as the numerical difference between numbers in OS and PFS at each time point. This can easily generate a sequence of negative results which are clearly meaningless and lead to erroneous results.

To overcome this problem, uncertainty in the HRs was addressed by use of linked variations in PFS and OS HRs, based on the estimated proportion of OS contributed by PFS leading to correlated random variables for PFS and OS. The proportions used for each regimen are shown in *Table 56*.

Synthesis of survival evidence: epidermal growth factor receptor mutation-positive population

Consistency of third-generation trial data

In order to include clinical trial evidence into a network for mixed-treatment comparison analysis it is important to establish compatibility of the populations studied and consistent treatment effects across trials. The many important trials of third-generation chemotherapy agents were carried out prior to widespread use of histology testing and before any genetic testing methods had been developed. However, third-generation trials continue to provide the bulk of evidence available to allow relative effectiveness of treatments to be assessed. The inclusion of PEM therapy in such an evidence network requires some confirmation that undifferentiated third-generation trials did not in fact conceal unsuspected important differences originating in different disease histology. A review of the available published trials identified four studies which reported multivariate statistical testing including histology as a candidate explanatory variable: Smit *et al.*[46] (PAX vs GEM), Gridelli *et al.*[45] (VNB vs GEM), Fossella *et al.*[44] (DOC vs VNB) and Scagliotti *et al.*[43] (GEM vs PAX vs VNB). In none of these trials did the authors report any significant influence of histology (squamous vs non-squamous) in determining effectiveness. On this basis it was considered appropriate to assume that trial evidence from trials of third-generation chemotherapy agents are equally applicable to patients with squamous disease as to those with non-squamous disease.

Inconsistency of third-generation trial data in gefitinib trials

However, the situation is quite different for patients with EGFR M+ disease, who predominantly have non-squamous histology. Only a limited number of trials with modest numbers of such patients have so far reported results. All of these compare EGFR-TKI products with third-generation chemotherapy regimens, but none compare with PEM + CIS which is indicated specifically for non-squamous (adenocarcinoma and large cell) disease. In order to consider the viability of incorporating all available third-generation trial evidence in an evidence network including GEF therapy, the PFS and OS profiles of the comparator arms in three GEF trials were compared with the profiles of the same treatments in the full third-generation network. This revealed that effectiveness of third-generation treatments was consistently far better in the EGFR M+ population than in the mixed populations (squamous and non-squamous disease), indicating that these patients have a better prognosis than other NSCLC patients, independent of the treatment received.

TABLE 56 Progression-free survival: OS ratios

Regimen	PFS : OS ratio
DOC	0.41
PAX	0.43
VNB	0.43
GEM	0.48
PEM	0.57

As a result it was considered inappropriate to carry out any meta-analysis involving third-generation trials not restricted to the EGFR M+ population and, therefore, no relative effectiveness estimates could be derived relating GEF to PEM (which would otherwise be a natural comparator for GEF). Instead, a separate analysis was undertaken restricted to the three reported GEF trials involving non-trivial numbers of EGFR M+ patients: IPASS,[15,64] North East Japan Gefitinib Study Group (NEJGSG)[63] and Western Japan Thoracic Oncology Group (WJTOG).[65] The synthesis method employed was weighted pooling of the PFS and OS Kaplan–Meier results for the GEF arm and for the comparator arm of the trials, and using these profiles directly to inform the model. The base case uses data from all three trials (despite mixing PAX and DOC comparator arms) and testing both PAX and DOC comparators in the model. Two alternative scenarios were also considered: A1 – pooling only the two trials involving a PAX comparator (IPASS[15,64] and NEJGSG[63]); and A2 – using the WJTOG[65] trial results directly in the model compared with DOC as comparator.

Other outcome variables

Patient disposition at disease progression

Following a PFS event (i.e. confirmed disease progression or death without prior disease progression) it is important to estimate the proportions of patients likely to receive additional systemic treatment or palliative care only. This requires values to be estimated for two parameters:

- the proportion of PFS events which are fatal
- the proportion of patients receiving at least second-line systemic treatment.

From these the proportion of patients receiving only palliative care after failure of first-line treatments can be derived.

Unfortunately, neither of these outcomes are routinely reported in published clinical trials, nor even in clinical study reports. Only two trials were found from which fatality figures could be deduced (Chen *et al.*[52] and Fukuoka *et al.*[64]) and since these relate to different patient populations and different interventions, pooling these results would be inappropriate. In practice, it was found that the main limitation on the fatality parameter is the need to ensure that the model logic does not generate negative estimates of PPS at any time for any treatment, and this imposes an effective maximum fatality between 20% and 25%. In the base-case analysis, 16% fatality is assumed with sensitivity analysis performed to explore the impact of uncertainty. The logic for the choice of 16% for this parameter was preserve the integrity of the PPS estimates by limiting the upper end of the PSA sampling range to effectively exclude any negative postprogression values being generated, assuming that the standard error of the parameter was 10% of the chosen mean value, and a maximum sampling point corresponded to 4 standard errors above the mean.

Patients receiving second-line systemic therapies were reported in 10 trials,[43–45,50,57,59,61,64,126,127] from which was obtained a pooled estimate of 45.2% for all populations, or 34.5% for the squamous disease population, 40.6% for the non-squamous disease population (including Scagliotti *et al*.[128] with the third-generation trials), 71.3% for DOC or PAX, and 77.5% for GEF in the EGFR M+ population (taken from the supplementary appendix by Mok *et al*.[15]).

Agent-specific adverse events

The costs and disutilities of treatment-related AEs are limited in the model to seven major categories (using the results of a multivariate model by Nafees *et al*.[116] described in detail below): diarrhoea, fatigue, neutropenia, febrile neutropenia, hair loss, nausea/vomiting and skin rash.

Reported incidence of grade 3/4 AEs in all published trials were pooled to obtain estimates of the proportion of patients suffering each event during chemotherapy. No attempt was made to carry out a more sophisticated meta-analysis as reporting of AEs was often incomplete and lacking in consistency.

Table 57 details the incidence rates obtained for each primary chemotherapy agent. No attempt has been made to distinguish between the types of PLAT treatment given in first-line doublets, as there were inadequate data in many cases to obtain meaningful estimates at that level of disaggregation.

Agent-specific response rates

The Nafees *et al*.[116] multivariate utility model also includes two levels of response to chemotherapy as predictive variables: 'responder' (either complete or partial response) and 'stable disease' (neither response nor disease progression). Estimates for these variables were obtained by pooling reported responses in published clinical trials in a similar manner to the derivation of AE incidence rates. The parameter values obtained are shown in *Table 58*.

TABLE 57 Pooled AE incidence rates (%) for primary chemotherapy agents

	AE						
Treatment	Diarrhoea	Fatigue	Febrile neutropenia	Hair loss	Nausea/vomiting	Neutropenia	Skin rash
DOC							
Mean (%)	6.4	9.0	2.9	0.0	20.4	62.1	0.0
95% CI	5.2 to 7.7	7.6 to 10.5	2.1 to 3.7	0.0 to 0.2	18.4 to 22.4	59.7 to 64.5	0.0 to 0.2
VNB							
Mean (%)	1.8	10.8	6.6	1.2	20.3	63.1	0.1
95% CI	1.2 to 2.6	9.3 to 12.3	5.4 to 7.9	0.7 to 1.8	18.4 to 22.2	60.8 to 65.4	0.0 to 0.5
PAX							
Mean (%)	2.3	7.1	4.9	0.0	13.5	57.4	0.4
95% CI	1.7 to 3.0	6.1 to 8.3	4.1 to 5.8	0.0 to 0.2	12.2 to 14.9	55.4 to 59.3	0.2 to 0.8
GEM							
Mean (%)	1.8	11.7	2.8	1.4	19.1	37.1	0.5
95% CI	1.2 to 2.4	10.2 to 13.3	2.1 to 3.7	0.9 to 1.9	17.6 to 20.6	35.3 to 39.0	0.2 to 0.9
PEM							
Mean (%)	1.3	6.7	1.3	0.0	11.2	20.6	0.1
95% CI	0.7 to 2.2	5.1 to 8.6	0.7 to 2.2	0.0 to 0.3	9.4 to 13.2	18.2 to 23.1	0.0 to 0.4
GEF							
Mean (%)	3.1	0.9	0.1	0.0	0.6	2.8	3.3
95% CI	2.0 to 4.4	0.4 to 1.6	0.0 to 0.5	0.0 to 0.3	0.2 to 1.3	1.8 to 4.1	2.2 to 4.7
ERL							
Mean (%)	1.5	3.3	0.0	0.0	0.7	0.0	8.0
95% CI	0.8 to 2.4	2.2 to 4.5	0.0 to 0.3	0.0 to 0.3	0.2 to 1.3	0.0 to 0.3	6.3 to 9.8

TABLE 58 Pooled response to chemotherapy rates (%) for primary chemotherapy agents

	Responders (%)		Stable disease (%)	
Treatment	Mean	95% CI	Mean	95% CI
DOC	26.7	24.5 to 29.0	39.1	36.7 to 41.6
PAX	27.5	25.6 to 29.3	34.1	32.1 to 36.1
VNB	28.6	26.4 to 31.0	36.5	34.1 to 39.0
GEM	27.3	25.4 to 29.3	38.5	36.4 to 40.6
PEM	30.6	27.4 to 33.9	41.2	37.7 to 44.7
PAX + DOC – (EGFR M+) – base case	38.1	32.7 to 43.6	44.7	39.1 to 50.3
PAX (EGFR M+) – A1	39.5	33.5 to 45.7	44.4	38.3 to 50.7
DOC (EGFR M+) – A2	32.2	21.0 to 44.5	45.8	33.3 to 58.5
GEF (EGFR M+) – base case	70.4	65.1 to 75.4	20.7	16.4 to 25.4
GEF (EGFR M+) – A1	72.4	66.6 to 77.8	18.3	13.7 to 23.3
GEF (EGFR M+) – A2	62.1	49.3 to 74.0	31.0	19.9 to 43.4

Chemotherapy acquisition costs

With the exception of the oral medications (GEF and ERL), all chemotherapy doses are calculated individually on the basis of the patient's body surface area. Calculations are carried out separately for males and females, and a weighted average cost is obtained using the relative proportions of recorded deaths from malignant neoplasm of trachea, bronchus and lung in England and Wales in 2010 (56.1% males, 43.9% females).[124] CIS costs are calculated for a single dose of 75 mg/m^2 each cycle. CARB costs are based on a dose of 400 mg/m^2 each cycle, with an alternative option based on flat dosing for a target AUC 5 level as described by Ekhart *et al.*[129] Sensitivity analysis by dosing calculation method should that using the alternative method produced minimal differences in any of the cost-effectiveness results described below.

Two sources are available as options to provide unit costs of purchasing chemotherapy drugs: the prices of generic medicines listed in the BNF (BNF 62,[130] September 2011) and the electronic market information tool[131] (eMIT) produced by the Commercial Medicines Unit of the Department of Health which provides estimated mean product prices for generic medicines drawn from information from about 95% of NHS trusts. *Table 59* summarises the unit cost data employed in the estimation of chemotherapy acquisition costs.

Chemotherapy costs are estimated per 21-day cycle for all regimens except GEF, where a fixed price per patient receiving more than two packs of tablets has been negotiated for use in England and Wales. These are shown in *Table 60*, for both BNF and eMIT prices; the base-case analysis is carried out using the BNF prices but, in general, eMIT prices may be considered more representative of the normal NHS cost environment.

TABLE 59 Unit acquisition costs for chemotherapy agents

Product	Vial content (mg)	BNF 62[130] price, mean (£)	eMIT[131] price, mean (£)
DOC[a]	20	154.61	90.20
	80	508.01	287.45
	140	720.10	285.09
GEM[a]	200	32.00	4.81
	1000	162.00	22.58
	2000	324.00	41.99
PAX[a]	30	66.85	5.02
	100	200.35	13.28
	150	300.52	12.45
	300	601.03	31.13
PEM	100	160.00	160.00
	500	800.00	800.00
VNB i.v.[a]	10	29.00	5.11
	50	139.00	23.09
VNB oral	20	43.98	43.98
	30	65.98	65.98
	80	175.92	175.92
GEF[b]	Per patient	12,200.00	12,200.00
CIS[a]	10	5.85	1.69
	50	17.00	3.58
	100	50.22	6.87
CARB[a]	50	22.04	2.03
	150	56.92	4.65
	450	168.85	13.50
	600	260.00	17.23
ERL	30 × 150 mg	1631.53	1631.53
	NHS discount	14.50%	14.50%
Dexamethasone[a]	50 × 2 mg	6.77	1.99
Chlorphenamine i.v.[a]	10	1.95	1.62
Ranitidine i.v.[a]	50	0.54	0.31
Hydroxocobalamin i.v.[a]	1	0.68	0.31
Folic acid[a]	90 × 400 µg	2.43	2.43

a Best generic price used.

b Patient Access Scheme price per patient applies only to patients receiving treatment beyond 60 days.

TABLE 60 Estimated acquisition cost per cycle of chemotherapy

Regimen		Estimated cost – BNF 62[130] prices (£)			Estimated cost – eMIT[131] prices (£)		
		Cycle 1	Cycles 2+	Per patient	Cycle 1	Cycles 2+	Per patient
First-line regimens							
1A	DOC i.v. + CIS	852.17	852.17	NA	367.52	367.52	NA
1B	DOC i.v. + CARB	1081.46	1081.46	NA	377.83	377.83	NA
2A	GEM i.v. + CIS	807.19	807.19	NA	112.16	112.16	NA
2B	GEM i.v. + CARB	1036.47	1036.47	NA	122.48	122.48	NA
3A	PAX i.v. + CIS	698.27	698.27	NA	49.16	49.16	NA
3B	PAX i.v. + CARB	927.55	927.55	NA	59.47	59.47	NA
4A	VNB i.v. + CIS	330.97	380.55	NA	58.55	66.78	NA
4B	VNB i.v. + CARB	560.25	609.83	NA	68.86	77.10	NA
5A	VNB oral + CIS	537.26	546.10	NA	496.50	505.34	NA
5B	VNB oral + CARB	766.54	775.38	NA	506.81	515.65	NA
6A	PEM i.v. + CIS	1535.40	1535.40	NA	1493.11	1493.11	NA
7	GEF oral	NA	NA	12,200.00	NA	NA	12,200.00
Second-line chemotherapy							
8	DOC i.v. monotherapy	799.66	799.66	NA	355.77	355.77	NA
9	ERL oral	1394.96	1394.96	NA	1394.96	1394.96	NA

NA, not applicable.

Administration cost of chemotherapy regimens

Clinical advisors from three specialist centres provided information on the context within which each regimen is normally delivered. There was general agreement that combination chemotherapy using CARB is always administered as a day-case episode, and that treatments involving only daily self-administered oral medication are prescribed at a monthly outpatient consultation. Combination regimens involving CIS show variation in clinical practice from 100% managed as day cases to up to 80% requiring an inpatient stay.

It was decided to assume 100% of these patients are managed as day cases, but to apply a sensitivity analysis in which 50% of patients require an additional overnight stay following administration.

The unit costs employed for chemotherapy administration, based on *NHS Reference Costs 2009–2010*,[132] are shown in *Table 61*.

TABLE 61 Unit costs of chemotherapy administration

Treatment setting	HRG code	Description	Mean (£)	Standard error (£)
Day case	SB14Z	Complex chemotherapy at first attendance	309.17	14.73
Day case	SB15Z	Subsequent doses of chemotherapy	284.45	8.95
Inpatient (short stay)	DZ17A	Respiratory neoplasms with complicating conditions	462.88	12.88
Outpatient	TCLFUSFF 370	Medical oncology	128.69	3.92

HRG, Healthcare Resource Group.

Health state costs

Costs have been estimated relating to patient monitoring and supportive care in three health states: in PFS (either during and following first-line chemotherapy or subsequently related to second-line chemotherapy), post progression when no active treatment is received, and for terminal care assumed to last on average for 14 days.

In both PFS and PPS, patients are expected to receive regular consultant-led outpatient consultations, and periodic diagnostic tests [chest radiography, CT scan and electrocardiogram (ECG)]. In addition, community-based supportive care is provided by the patient's general practitioner (GP) (in surgery, or at home) and community nursing staff. In the terminal phase, care is likely to be more intensive, with the package varying by the chosen setting.

Table 62 details the mean volumes of each resource assumed and *Table 63* summarises the unit costs employed together with the relevant sources.

Adverse event costs

The costs of treating grade 3/4 chemotherapy-related AEs are spread over 12 weeks (four cycles) and estimated using *NHS Reference Costs for 2009–2010*,[132] as follows.

Diarrhoea

It is assumed that a typical patient will have two hospital admissions during chemotherapy, corresponding to Healthcare Research Group (HRG) code FZ48C (malignant general abdominal disorders of length of stay ≤ 1 day) as a non-elective short-stay episode, each costing £443.54.

Fatigue

It is assumed that a typical patient will have one hospital admission during chemotherapy, corresponding to HRG code WA17X (other admissions related to neoplasms with intermediate complicating conditions) as a non-elective long-stay episode of 8–9 days costing £2536.95.

Hair loss

It is assumed that there are no hospital episodes related to the AE and no direct costs are incurred.

Nausea/vomiting

It is assumed that a typical patient will have two hospital admissions during chemotherapy, corresponding to HRG code FZ48C (malignant general abdominal disorders of length of stay ≤ 1 day) as a non-elective short-stay episode, each costing £443.54.

TABLE 62 Estimated health-care resource use per patient for disease monitoring and supportive care in PFS, PPS and during the terminal phase

Resource	PFS	PPS	Terminal care	Source
Outpatient visit	9.61 pa	7.91 pa	–	Big Lung Trial[133]
Chest radiography	6.79 pa	6.50 pa	–	Big Lung Trial[133]
CT scan (chest)	0.62 pa	0.24 pa	–	Big Lung Trial[133]
CT scan (other)	0.36 pa	0.42 pa	–	Big Lung Trial[133]
ECG	1.04 pa	0.88 pa	–	Big Lung Trial[133]
Hospital/hospice episode	–	–	9.66 days	Average stay for non-elective long-stay inpatient episode plus average inpatient excess days for HRG DZ17A – *NHS Reference Costs 2009–2010*[132]
Community nurse visit	8.70 visits (20 minutes) pa	8.70 visits (20 minutes) pa	28 hours (2 hours per day)	Appendix 1 of NICE Guideline CG81[134] Marie Curie report[135]
Clinical nurse specialist	12 hours contact time pa	12 hours contact time pa		Appendix 1 of NICE Guideline CG81[134]
GP surgery	12 consultations pa	–	–	Appendix 1 of NICE Guideline CG81[134]
GP home visit	–	26.09 pa (fortnightly)	Seven visits (alternate days)	Marie Curie report[135]
Therapist visit	–	26.09 pa (fortnightly)	-	Appendix 1 of NICE Guideline CG81[134]
Macmillan nurse	–		50 hours	Marie Curie report[135]
Drugs/equipment	–	–	As required	Marie Curie report[135]
Location of terminal care	–	–	Hospital 55.8% Hospice 16.9% Home 27.3%	Office for National Statistics death tables 5.2 and 12[124]

pa, per annum.

Skin rash

It is assumed that a typical patient will have one additional outpatient consultation during chemotherapy for this condition. A weighted average reference cost of £113.03 is used, based on codes 370 (medical oncology) and 800 (clinical oncology).

Neutropenia (non-febrile)

It is assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy. The cost per episode is £537.52 and is estimated from the weighted average of mean costs for HRG code WA02W (disorders of immunity without HIV/AIDS with complicating condition) across non-elective long- and short-stay episodes and day-case admissions.

Febrile neutropenia

The NICE Decision Support Unit report on the cost of febrile neutropenia has been updated for current *NHS Reference Costs 2009–2010*.[132] This assumes 1.4 episodes per patient during the four cycles (12 weeks) of chemotherapy. The estimated cost per patient suffering febrile neutropenia is £6260.

In the model, the estimated cost per patient of chemotherapy-related AEs is shown in *Table 64*.

TABLE 63 Unit costs of disease monitoring and supportive care

Resource	Unit cost	Source
Outpatient follow-up visit	£101.43	*NHS Reference Costs 2009–2010*, HRG code TCLFUSFF 800 clinical oncology[132]
Chest radiography	£24.04	NICE technology appraisal TA199; TAG report, p. 328[136]
CT scan (chest)	£145.83	*NHS Reference Costs 2009–2010*, HRG code RA12Z (two areas with contrast)[132]
CT scan (other)	£162.25	*NHS Reference Costs 2009–2010*, HRG code RA13Z (three areas with contrast)[132]
ECG	£32.69	*NHS Reference Costs 2009–2010*, code DA01 – direct access ECG (12 lead)[132]
Community nurse	£78.00 per hour	PSSRU *Unit Costs of Health and Social Care 2010*, p. 159 cost per hour spent on home visits (including qualification)[137]
Clinical nurse specialist	£91.00 per contact hour	PSSRU *Unit Costs of Health and Social Care 2010*, p. 162 cost per contact hour (including qualification)[137]
GP surgery visit	£36.00	PSSRU *Unit Costs of Health and Social Care 2010*, p. 167 cost per surgery visit (11.7 minutes, including direct care staff)[137]
GP home visit	£120.00	PSSRU *Unit Costs of Health and Social Care 2010*, p. 167 cost per home visit (23.4 minutes, including travel time)[137]
Therapist	£42.00	PSSRU *Unit Costs of Health and Social Care 2010*, p. 177 cost per hour (including training)[137]
Terminal care inpatient care	£2655.55 + 0.92 excess days at £196.61 per day	*NHS Reference Costs 2009–2010*, code DZ17A (respiratory neoplasms with major CC), non-elective inpatient (long stay – episode/excess days)[132]
Terminal care in hospice	25% increase on hospital IP care	Assumption
Macmillan nurse	66.7% of community nurse cost	Assumption
Drugs and equipment	£500	Marie Curie report figure of £240 increased for inflation[135]

CC, complications; IP, inpatient; PSSRU, Personal Social Services Research Unit; TAG, Technology Assessment Group.

Health valuation estimation

Ideally, the utility of NSCLC patients should be informed by data obtained directly from the relevant patient population relating to their perceived condition at all phases of the treatment pathway covered by the economic model. Unfortunately, this is practically and ethically impractical for patients suffering advanced disease with severe symptoms (arising from either the natural course of the disease or related to treatments received) and who have generally very limited life expectancy. A recent study in the Netherlands[33] attempted to obtain such data (using the EQ-5D instrument) from an observational study of NSCLC patients treated between 2004 and 2007, and surviving to 2008. Unfortunately, this patient sample is not representative of the populations considered in this model (locally advanced and metastatic NSCLC) since only 44% of patients had received any chemotherapy, only 41% had stage III/IV disease and only 14% had local/regional or metastatic recurrent disease at the time of the survey. Clearly, the results obtained are dominated by patients who were diagnosed at an early stage and had successful surgery, potentially biasing numeric estimates of utility toward higher values.

The only alternative to direct measurement of patient symptoms for estimating utility is via a structure sample of the general public valuing a set of typical patient scenarios, representing the range of likely conditions experienced by NSCLC patients during their remaining lifetime. Two such recent studies have been identified. Doyle *et al.*[138] recruited 101 volunteers from the general public in the London (UK) area,

TABLE 64 Estimated cost per patient of chemotherapy-related AEs

	Product cost (£)						
AE	DOC	VNB	PAX	GEM	PEM	GEF	ERL
Diarrhoea	57	16	20	16	12	27	14
Fatigue	229	273	181	297	171	22	83
Febrile neutropenia	179	411	310	172	83	8	0
Hair loss	0	0	0	0	0	0	0
Nausea/vomiting	181	180	120	170	100	5	6
Neutropenia	129	131	119	77	43	6	0
Skin rash	0	0	2	2	0	11	27
Total AE cost	773	1011	751	733	409	80	129

who were asked to value six typical health states experienced by advanced NSCLC patients, using the standard gamble method. This allowed estimation of a mean utility value for patients with stable disease on treatment, as well as the incremental effect of response to treatment, and also the incremental disutility of three common symptoms (cough, dyspnoea and pain). Although promising, this study provides only limited results which are insufficient to populate all the health states and important AEs which feature in the current model.

The utility scheme which has been adopted for use in the current model is that described in a paper published in 2008 by Nafees *et al*.[116] This also uses the standard gamble method and employed 100 volunteers from the UK general population. In this case a more extensive set of scenarios were used (17 specific disease health states plus two 'anchor' states), developed with the help of a panel of oncologists and designed specifically to address a range of the most common severe AEs experienced by advanced NSCLC patients. A mixed-model analysis yielded simultaneous utility estimates for three health states (responding to treatment, stable disease and progressive disease) together with incremental disutility values for seven common serious (grade 3/4) AEs – neutropenia, febrile neutropenia, fatigue, diarrhoea, nausea and vomiting, hair loss (alopecia) and rash.

Applying the treatment-specific AE incidence rates (see *Table 57*) and treatment response rates (see *Table 58*) to the Nafees *et al*.[116] utility model yields a full set of health state utilities for each treatment option as shown in *Table 65*. The utility for the terminal period (last 2 weeks of life) was obtained by use of results reported for average EQ-5D scores relative to the time prior to death (figure 3 of the van der Hout *et al*. 2006 study[139] of palliative radiotherapy in patients with NSCLC) and the utility estimate for PPS 2 was adjusted to reflect progressive disease prior to the terminal period.

Discounting

In the base-case analysis both costs and outcomes are discounted at 3.5% per annum in line with NICE guidance.[140] Sensitivity analyses are reported for discount rates between 0% and 6%.

Time horizon

A lifetime perspective is taken in the model, which projects all costs, patient events and costs to a maximum of 10 years, at which time it is assumed all patients will have died.

Modelling assumptions

First-line chemotherapy regimens with the same primary agent but different PLAT therapy (A vs B) differ only in terms of treatment costs. Although meta-analyses[84,85] found some minor differences in outcomes

TABLE 65 Estimated health-related utility values using the Nafees *et al.*[116] model

First-line chemotherapy	PFS 1 on treatment	PFS 1 post treatment	PPS 1 following first progression
DOC	0.5833	0.6610	0.4896
PAX	0.5929	0.6618	0.4896
VNB	0.5801	0.6617	0.4896
GEM	0.6060	0.6612	0.4896
PEM	0.6307	0.6614	0.4896
GEF (EGFR+)	0.6625	0.6686[a]	0.4896
PAX (EGFR+)	0.5934	0.6623	0.4896
Second-line chemotherapy	**PFS 2**	**PPS 2**	**Terminal period (2 weeks)**
DOC	0.5927 (on chemotherapy) 0.6559 (post chemotherapy)	0.4275	0.0686
ERL	0.6524	0.4275	0.0686

a This estimate is not employed in the EGFR M+ model as all patients continue on treatment until disease progression.

favouring CIS over CARB, and in AEs (more thrombocytopenia with CARB, and more nausea/vomiting and nephrotoxicity with CIS), on balance it was concluded that the evidence suggested only a limited net difference in patient benefit, unlikely to influence the results of any comparisons.

Results for population 1 (patients with squamous disease)

Deterministic analysis

Base case (*British National Formulary* prices)

Summary model results for the base-case analysis using BNF drug acquisition prices are shown in *Tables 66* and *67* (costs and QALYs, respectively). For all primary chemotherapy agents, use of CARB is associated with slightly higher costs than use of CIS. Outcomes vary between regimens, between DOC (best) and VNB (worst). *Figure 30* indicates that two CIS regimens lie on the efficiency frontier: PAX (3A) and DOC (1A), with a pair-wise ICER of £27,159 per QALY gained for 1A (DOC + CIS) compared with 3A (PAX + CIS). VNB is more expensive and less effective than PAX and is therefore dominated, whereas GEM is more expensive and less effective than DOC.

Alternative scenario (electronic market information tool prices)

Applying mean NHS negotiated prices in place of published list prices leads to substantial reductions in acquisition costs, but has no other effects on costs or outcomes. The revised cost estimates are shown in *Table 68*.

The corresponding efficiency frontier (*Figure 31*) now features three regimens, two using CARB as the PLAT component. The estimated ICER for GEM + CARB compared with PAX + CARB is £34,605 per QALY gained, and for DOC + CIS compared with GEM + CARB is £49,065 per QALY gained. However, there is minimal difference between the PLAT compounds when used in combination with DOC. VNB remains dominated because of its inferior outcomes. The general change to preferring CARB doublets in this scenario arises because with heavy price discounting the importance of NHS administration costs to the overall cost is

TABLE 66 Deterministic estimated cost per patient for base-case analysis (BNF prices): patients with squamous disease

Regimen code		Drug acquisition (£)	Drug admin. (£)	AEs (£)	Supportive care (£)	Terminal care (£)	Total cost (£)
1	A	4876	968	661	6542	3812	16,859
	B	5636	968	661	6542	3812	17,619
2	A	4250	2966	738	5288	3829	17,070
	B	5067	2167	738	5288	3829	17,088
3	A	3715	1387	690	5325	3833	14,950
	B	4471	1105	690	5325	3833	15,424
4	A	3076	2465	896	5023	3841	15,302
	B	3836	2012	896	5023	3841	15,609
5	A	3180	2465	896	5023	3841	15,405
	B	3939	2012	896	5023	3841	15,712

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; A, combined with CIS; admin., administration; B, combined with CARB.

TABLE 67 Deterministic estimated QALYs per patient for base-case analysis (BNF prices): patients with squamous disease

Regimen code		Time in PFS 1	Time after PD 1	OS	QALYs in PFS 1	QALYs after PD 1	Total QALYs
1	A/B	0.4338	0.7261	1.1599	0.2729	0.3288	0.6017
2	A/B	0.5341	0.5007	1.0348	0.3423	0.2267	0.5690
3	A/B	0.4439	0.5517	0.9956	0.2815	0.2498	0.5314
4	A/B	0.4392	0.5121	0.9512	0.2760	0.2319	0.5079
5	A/B	0.4392	0.5121	0.9512	0.2760	0.2319	0.5079

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; A, combined with CIS; B, combined with CARB; PD, progressive disease.

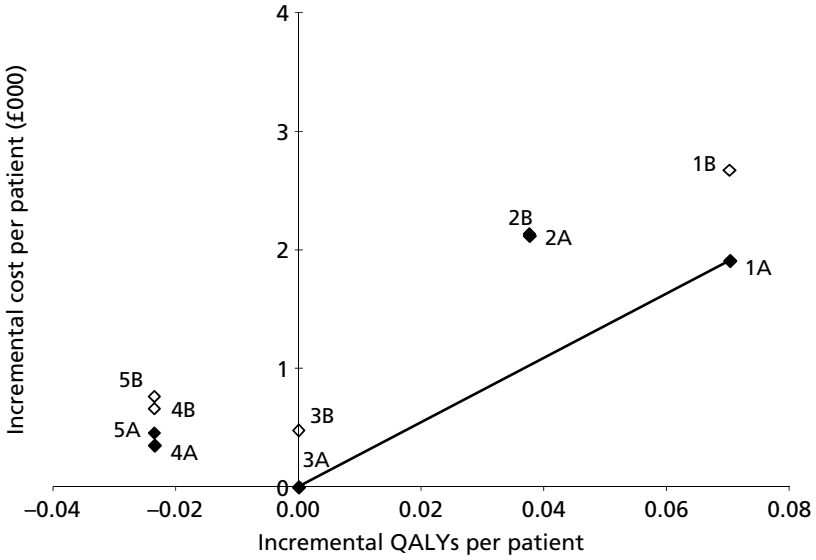

FIGURE 30 Cost-effectiveness plane for deterministic base-case analysis (BNF prices): patients with squamous disease.

TABLE 68 Deterministic estimated cost per patient for alternative analysis (eMIT prices): patients with squamous disease

Regimen code		Drug acquisition (£)	Total cost (£)
1	A	3268	15,251
	B	3302	15,285
2	A	1590	14,410
	B	1627	13,648
3	A	1359	12,594
	B	1394	12,346
4	A	2609	14,835
	B	2644	14,416
5	A	2828	15,054
	B	2863	14,635

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; A, combined with CIS; B, combined with CARB.

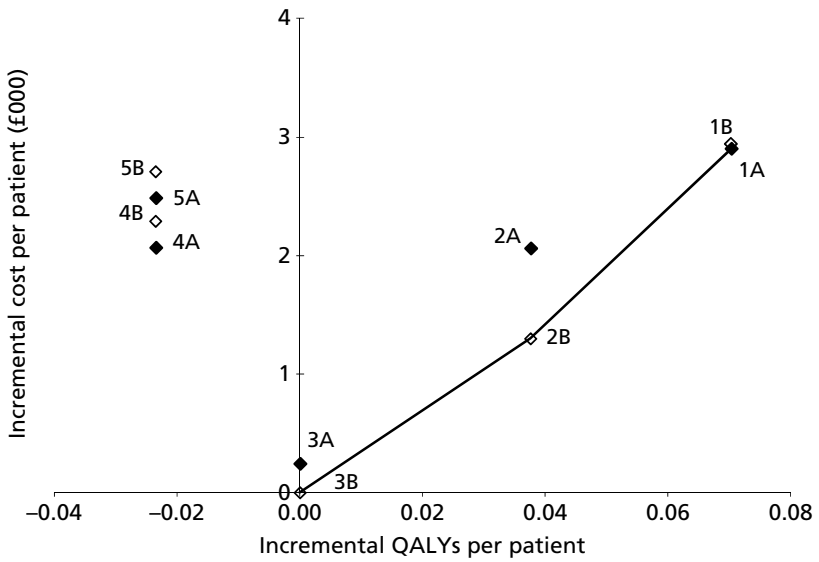

FIGURE 31 Cost-effectiveness plane for deterministic alternative analysis (eMIT prices): patients with squamous disease.

increased relative to acquisition costs, so that the less demanding CARB regimens which are more likely to be deliverable in a day-case setting incur lower delivery costs.

Sensitivity analysis

A full univariate sensitivity analysis was carried out to explore the relative importance of uncertainty in each parameter to the estimated ICER of DOC + CIS compared with PAX + CIS using the base-case scenario, and varying parameter values across the 95% CI. The main exceptions are the proportions of patients receiving chemotherapy in a day-case setting, and the proportions of second-line patients receiving ERL (rather than DOC). In these cases an absolute variation of ± 10% was applied, equivalent to a relative variation of about 20%. The only parameter where a 10% relative variation was applied is the proportion of PFS events

which are fatal; as previously mentioned, this parameter is not amenable to much wider variation if it is to avoid taking both invalid lower and upper values.

The results for 20 variables which most affect the estimated ICER are shown in *Figure 32*.

The estimated (correlated) HRs for PFS and OS for the comparator versus PAX are clearly the dominant variables in the model. Next most influential are the estimated utility parameters for progressive and stable disease in the Nafees *et al*. utility model.[116] Thereafter, uncertainty in type of second-line therapy, and in the mode and cost of chemotherapy administration are influential.

Probabilistic sensitivity analysis

A PSA was performed for the base-case scenario including all parameters for which uncertainty could be characterised statistically (details are shown in *Appendices 30* and *31*). CIS was assumed as the PLAT component in all regimens, and i.v. VNB was preferred to the oral formulation. The PSA was repeated for the alternative scenario (eMIT prices), using CARB throughout. The summary results of both scenarios for the four treatments are shown in *Table 69*, and the cost-effectiveness acceptability plots are displayed in *Figures 33* and *34*. The PSA repeated the favourable result for GEM suggested in the deterministic analysis when eMIT drug prices are assumed, indicating that only VNB doublets do not lie on the efficiency frontier.

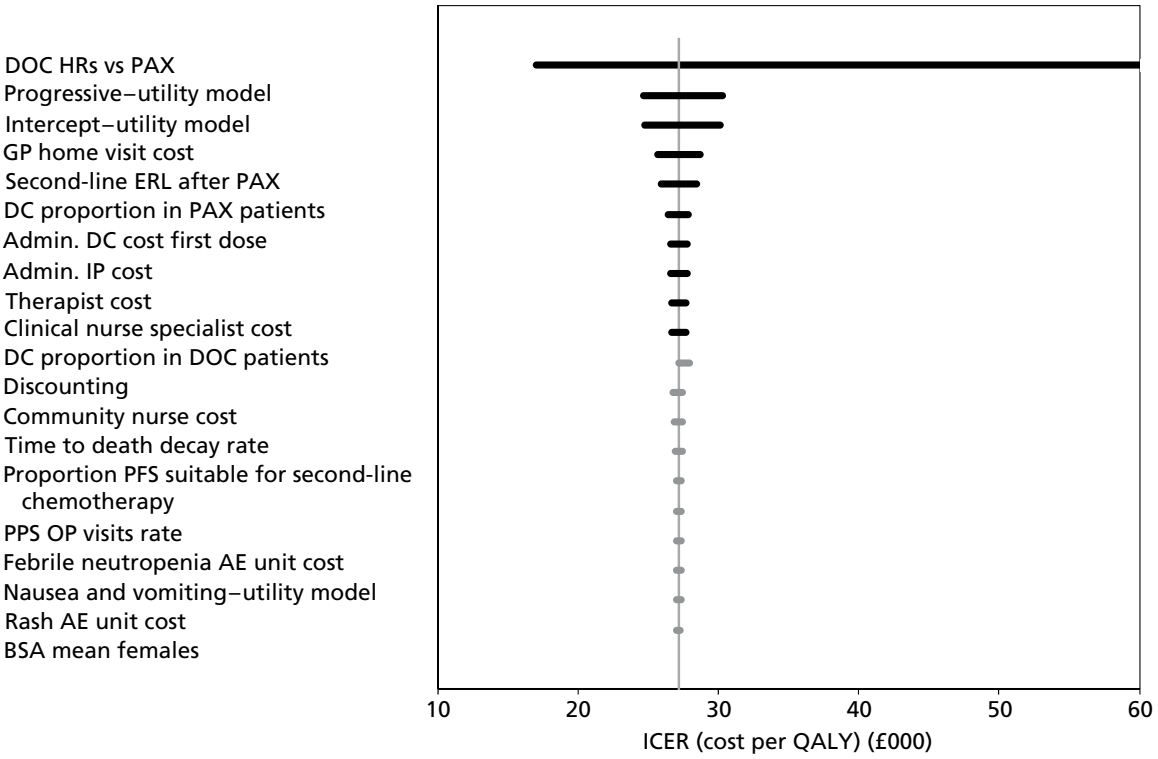

FIGURE 32 Univariate sensitivity analysis of base-case scenario comparison of DOC to PAX (deterministic ICER = £27,159/QALY), showing 20 variables with the widest uncertainty range: patients with squamous disease. admin., administration; BSA, body surface area; DC, day case; IP, inpatient; OP, outpatient.

TABLE 69 Summary results of PSA for base-case and alternative scenarios: patients with squamous disease

		Base-case scenario		Alternative scenario	
Regimen	PSA result	Mean	Incremental	Mean	Incremental
DOC	Total cost (£)	17,112	1796	15,244	2877
	Total QALYs	0.6017	+0.0704	0.6017	+0.0704
GEM	Total cost (£)	17,572	2257	13,713	1347
	Total QALYs	0.5691	+0.0378	0.5691	+0.0378
PAX	Total cost (£)	15,315	0	12,367	0
	Total QALYs	0.5313	0	0.5313	0
VNB	Total cost (£)	15,619	304	14,666	2299
	Total QALYs	0.5103	–0.0211	0.5103	–0.0211
ICER		£25,533/QALY DOC vs PAX		£35,664/QALY GEM vs PAX £46,939/QALY DOC vs GEM	

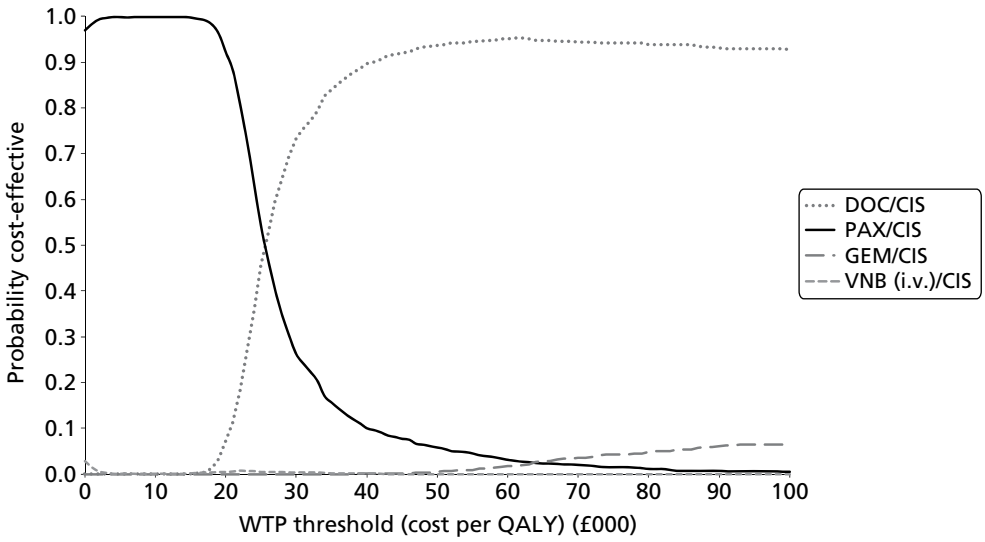

FIGURE 33 Probabalistic sensitivity analysis for base-case scenario, assuming CIS as PLAT component, and i.v. VNB: patients with squamous disease. WTP, willingness to pay.

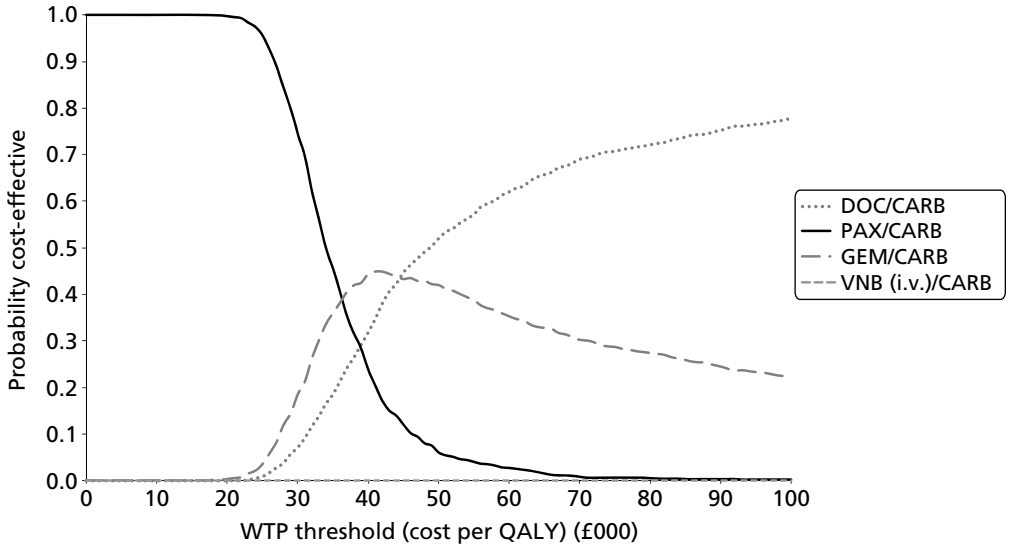

FIGURE 34 Probabalistic sensitivity analysis for alternative scenario (eMIT prices), assuming CARB as PLAT component, and i.v. VNB: patients with squamous disease. WTP, willingness to pay.

Summary of results for population 1 (patients with squamous disease)

- In both deterministic and probabilistic analyses for both the base-case and alternative pricing scenarios, VNB doublets yield the least patient benefit (as measured by expected discounted QALYs), and are not the least expensive option. As a result, VNB cannot be considered to provide either optimal effective or cost-effective chemotherapy treatment.
- PAX doublets are consistently minimum cost options and therefore represent the initial 'good value' treatment, only to be supplanted if an alternative option yields greater benefit at an acceptable 'willingness-to-pay' (WTP) threshold.
- The choice of preferred alternative main agent to PAX generally favours DOC over GEM as its greater effectiveness appears to outweigh the additional acquisition cost, although both lie on the efficiency frontier.

Three more general observations may also be made on the basis of these results.

1. The difference in incremental QALYs gained between the treatments reflect only very marginal differences in benefit.
2. The sensitivity of the results to the general level of drug prices especially relating to the choice of PLAT compound indicates that in a competitive market, which has driven most generic prices down to very low levels, the price of drugs becomes less important than differences in the cost of drug administration and in the relative cost of AEs. Thus, achieving increased efficiency under these circumstances involves maximising the likelihood that patients can receive chemotherapy without recourse to inpatient admission.
3. The differences in estimated ICERs between the deterministic and probabilistic analyses is predominantly attributable to the fact that the greatest source of parameter uncertainty relates to estimated HRs which are subject to non-linear (logarithmic) distributions, leading to asymmetric cost-effectiveness results. Under these circumstances, the probabilistic results should be considered more reliable.

Results for population 2 (patients with non-squamous disease)

Deterministic analysis

Base case (*British National Formulary* prices)

The summary model results for the base-case analysis using BNF drug acquisition prices are shown in *Tables 70* (costs) and *71* (costs and QALYs, respectively). For all primary chemotherapy agents, use of CARB is associated with slightly higher costs than use of CIS. Outcomes vary between regimens, between PEM (best) and VNB (worst). *Figure 35* indicates that two CIS regimens lie on the efficiency frontier: PAX (3A) and PEM (6A), with a pair-wise ICER of £26,175 per QALY gained for 6A (PEM + CIS) compared with 3A (PAX + CIS). However, it is apparent that DOC + CIS lies very close to the frontier and should be considered of similar cost-effectiveness. VNB is more expensive and less effective than PAX and is therefore dominated, whereas GEM is less effective than DOC and with similar net incremental cost per patient.

TABLE 70 Deterministic estimated cost per patient for base-case analysis (BNF prices): patients with non-squamous disease

Regimen code		Drug acquisition (£)	Drug admin. (£)	AEs (£)	Supportive care (£)	Terminal care (£)	Total cost (£)
1	A	4876	968	661	6548	3812	16,865
	B	5637	968	661	6548	3812	17,626
2	A	4251	2966	738	5281	3829	17,065
	B	5067	2167	738	5281	3829	17,083
3	A	3715	1387	690	5325	3833	14,950
	B	4471	1105	690	5325	3833	15,424
4	A	3076	2465	896	5028	3841	15,306
	B	3836	2012	896	5028	3841	15,613
5	A	3179	2465	896	5028	3841	15,409
	B	3939	2012	896	5028	3841	15,716
6	A	7434	1522	505	6980	3790	20,231
	B	8297	1522	505	6980	3790	21,094

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; 6, PEM; A, combined with CIS; admin., administration; B, combined with CARB.

TABLE 71 Deterministic estimated QALYs per patient for base-case analysis (BNF prices): patients with non-squamous disease

Regimen code		Time in PFS 1	Time after PD 1	OS	QALYs in PFS 1	QALYs after PD 1	Total QALYs
1	A/B	0.4341	0.7268	1.1609	0.2730	0.3291	0.6022
2	A/B	0.5348	0.4995	1.0343	0.3427	0.2262	0.5689
3	A/B	0.4439	0.5517	0.9956	0.2815	0.2498	0.5314
4	A/B	0.4389	0.5128	0.9517	0.2759	0.2322	0.5081
5	A/B	0.4389	0.5128	0.9517	0.2759	0.2322	0.5081
6	A/B	0.6496	0.6777	1.3274	0.4231	0.3100	0.7331

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; 6, PEM; A, combined with CIS; B, combined with CARB; PD, progressive disease.

Alternative scenario (electronic market information tool prices)

Applying mean NHS negotiated prices in place of published list prices, leads to substantial reductions in acquisition costs, but has no other effects on costs or outcomes. The revised cost estimates are shown in *Table 72*.

The corresponding efficiency frontier (*Figure 36*) now features three regimens: PAX + CARB, GEM + CARB and PEM + CIS. The estimated ICER for GEM + CARB compared with PAX + CARB is £34,542 per QALY gained and for PEM + CIS compared with GEM + CARB is £37,608 per QALY gained. VNB remains dominated because of its inferior outcomes. As in the squamous disease population results, the general

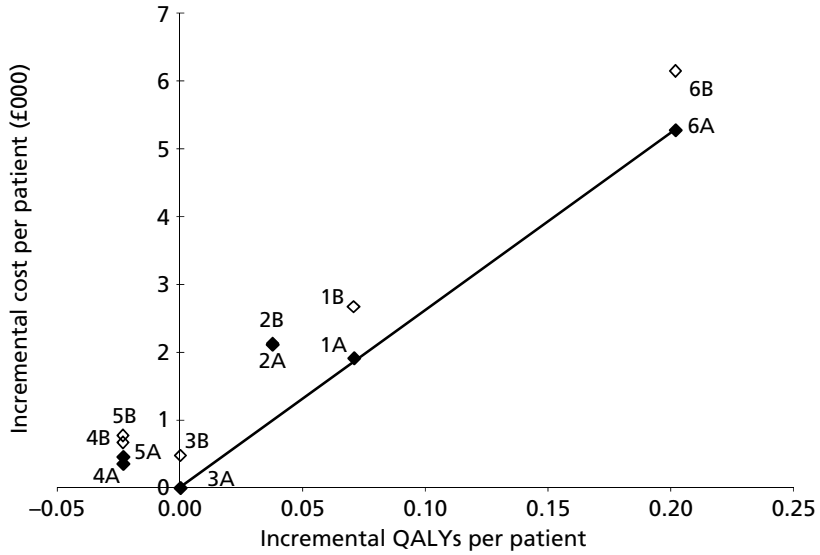

FIGURE 35 Cost-effectiveness plane for deterministic base-case analysis (BNF prices): patients with non-squamous disease.

TABLE 72 Deterministic estimated cost per patient for alternative analysis (eMIT prices); patients with non-squamous disease

Regimen code		Drug acquisition (£)	Total cost (£)
1	A	3268	15,257
	B	3302	15,292
2	A	1590	14,405
	B	1627	13,642
3	A	1359	12,594
	B	1394	12,346
4	A	2609	14,839
	B	2644	14,420
5	A	2828	15,058
	B	2862	14,639
6	A	7022	19,819
	B	7061	19,857

1, DOC; 2, GEM; 3, PAX; 4, VNB oral; 5, VNB i.v.; 6, PEM; A, combined with CIS; B, combined with CARB.

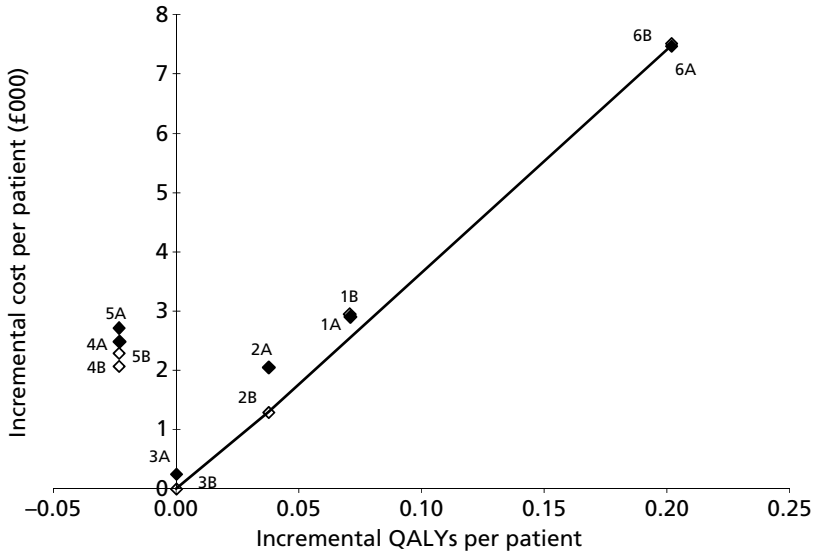

FIGURE 36 Cost-effectiveness plane for deterministic alternative analysis (eMIT prices): patients with non-squamous disease.

change to preferring CARB doublets in this scenario arises because with heavy price discounting the importance of NHS administration costs to the overall cost is increased relative to acquisition costs.

Sensitivity analysis

A full univariate sensitivity analysis was carried out to explore the relative importance of uncertainty in each model parameter to the estimated ICER of PEM + CIS compared with PAX + CIS using the base-case scenario, and varying most parameter values across the 95% CI. In other variables a notional absolute range of ± 10% of the estimated value was used. The results for 20 variables which most affect the estimated ICER are shown in *Figure 37*.

The estimated (correlated) HRs for PFS and OS for PEM compared with PAX are clearly the dominant variables in the model. Next most influential are the estimated utility parameters for progressive and stable disease in the Nafees *et al*.[116] utility model. Other parameters make only minor contributions to uncertainty in the estimated ICER.

Probabilistic sensitivity analysis

A PSA was performed for the base-case scenario including all parameters for which uncertainty could be characterised statistically. CIS was assumed as the PLAT component in all regimens, and i.v. VNB was preferred to the oral formulation. The PSA was repeated for the alternative scenario (eMIT prices), using CARB throughout, except for PEM.

The summary results of both scenarios for the four treatments are shown in *Table 73* and the cost-effectiveness acceptability plots are displayed in *Figures 38* and *39*.

Summary of results for population 2 (patients with non-squamous disease)

The addition of a PEM doublet to the four third-generation chemotherapy agents changes the relationship between the regimens, owing to the clear outcome advantage of PEM therapy in terms of improved expected survival for patients with non-squamous disease. However, the high price of branded PEM compared with the other drugs (in most cases available generically) means that PEM is only preferred on cost-effectiveness grounds if the WTP threshold is set > £37,000 per QALY (or £50,000 per QALY if sampled NHS contract prices are assumed). This means that PAX remains a viable treatment (and possibly GEM and DOC). However, VNB is clearly not cost-effective in either scenario.

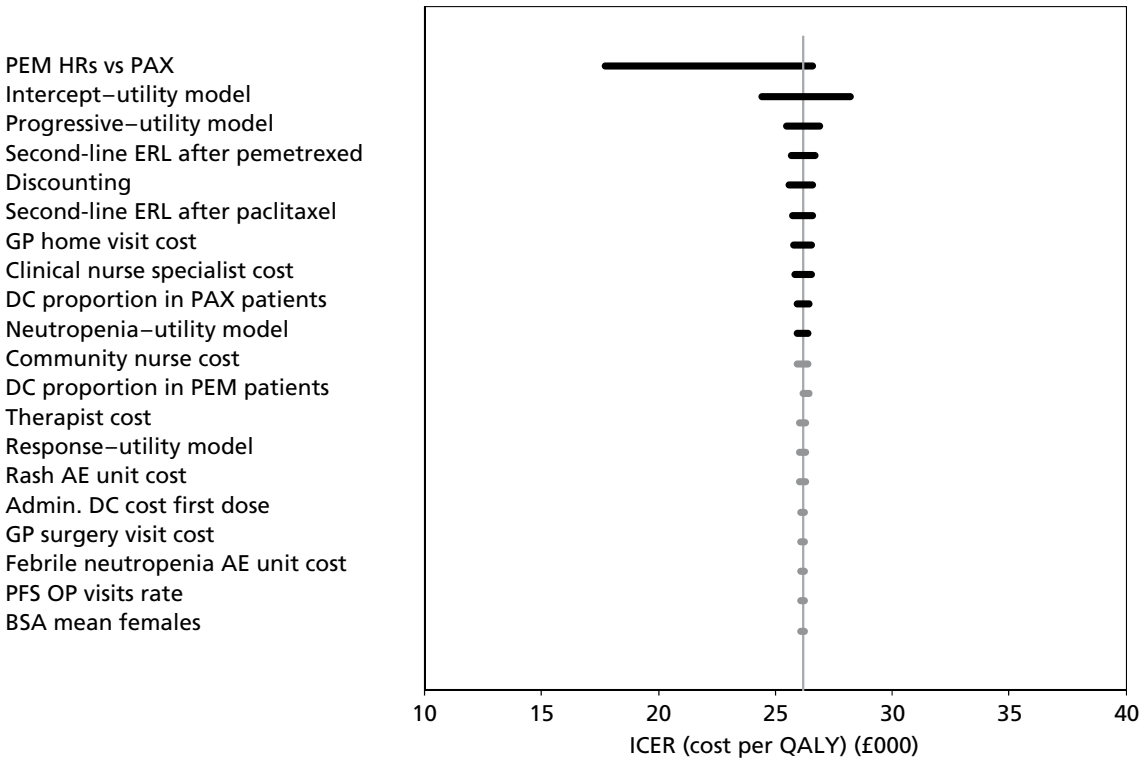

FIGURE 37 Univariate sensitivity analysis of alternative scenario comparison of PEM to PAX (deterministic ICER = £26,175/QALY), showing 20 variables with the widest uncertainty range: patients with non-squamous disease. admin., administration; BSA, body surface area; DC, day case; OP, outpatient.

TABLE 73 Summary results of PSA for base-case and alternative scenarios: patients with non-squamous disease

		Base-case scenario		Alternative scenario	
Regimen	PSA result	Mean	Incremental	Mean	Incremental
DOC	Total cost (£)	17,153	1838	15,285	2918
	Total QALYs	0.6044	+0.0731	0.6044	+0.0731
GEM	Total cost (£)	17,561	2246	13,702	1335
	Total QALYs	0.5687	+0.0373	0.5687	+0.0373
PAX	Total cost (£)	15,315	0	12,367	0
	Total QALYs	0.5313	0	0.5313	0
VNB	Total cost (£)	15,617	302	14,664	2297
	Total QALYs	0.5101	–0.0212	0.5101	–0.0212
PEM	Total cost (£)	21,284	5968	20,803	8436
	Total QALYs	0.7137	+0.1824	0.7137	+0.1824
ICER		£25,155/QALY DOC vs PAX £37,779/QALY PEM vs DOC		£35,776/QALY GEM vs PAX £44,293/QALY DOC vs GEM £50,470/QALY PEM vs DOC	

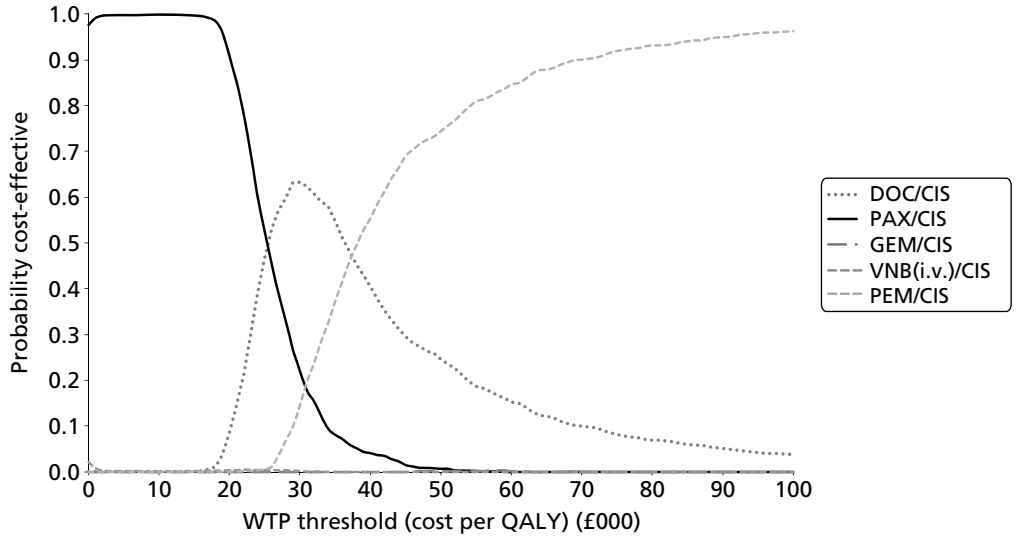

FIGURE 38 Probabalistic sensitivity analysis for base-case scenario, assuming CIS as PLAT component, and i.v. VNB: patients with non-squamous disease.

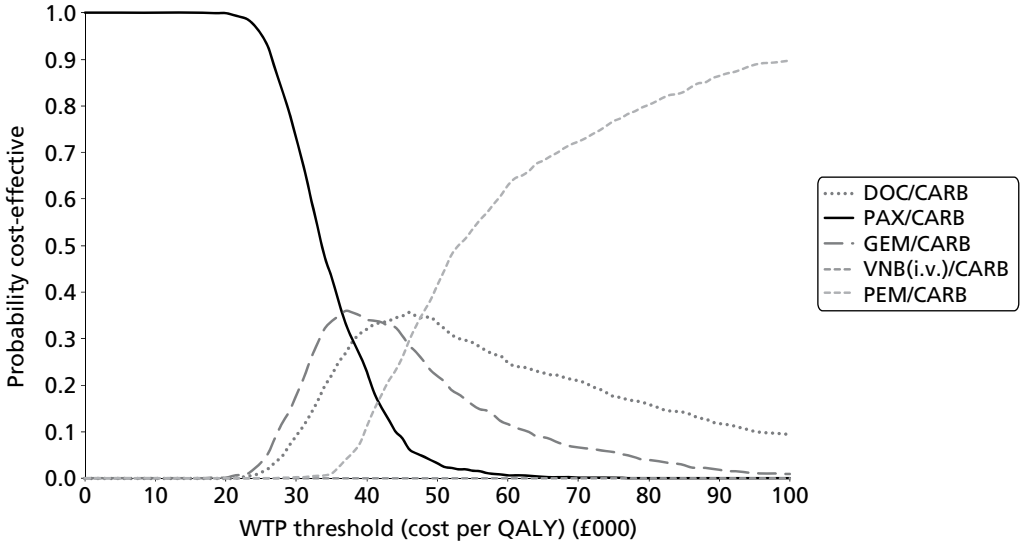

FIGURE 39 Probabalistic sensitivity analysis for alternative scenario (eMIT prices), assuming CARB as PLAT component except for PEM, and i.v. VNB: patients with non-squamous disease.

Results for population 3 (epidermal growth factor receptor mutation positive)

Deterministic analysis

Base case (*British National Formulary* prices)

The summary model results for the base-case analysis using BNF drug acquisition prices are shown in *Tables 74* and *75* (costs and QALYs, respectively). For both primary chemotherapy agents (DOC and PAX), use of CARB is associated with slightly higher costs than use of CIS. Outcomes vary between regimens: in terms of expected survival chemotherapy appears to have a small advantage over GEF (about 2 weeks) but GEF provides a modest improvement in expected QALYs compared with chemotherapy (0.0786), owing to the extended period prior to disease progression. The slightly higher cost per patient and poorer outcomes of DOC regimens compared with PAX excludes them from consideration for cost-effectiveness. The estimated deterministic ICER for GEF compared with PAX + CIS is £57,440 per QALY gained.

Base case (electronic market information tool prices)

Applying mean NHS negotiated prices in place of published list prices, leads to substantial reductions in acquisition costs for chemotherapy treatments, but has no other effects on costs or outcomes. The revised cost estimates are shown in *Table 76*. Deterministic estimated cost per patient for base-case analysis using eMIT prices.

Using PAX in combination with CARB now offers the minimum cost regimen for comparison with GEF. The estimated ICER for GEF compared with PAX + CARB is £85,848 per QALY gained

Sensitivity analysis

A full univariate sensitivity analysis was carried out to explore the relative importance of uncertainty in each model parameter to the estimated ICER of PAX + CIS compared with GEF using the base-case scenario with BNF prices, and varying most parameter values across the 95% CI. In other variables, a notional absolute

TABLE 74 Deterministic estimated cost per patient for base-case analysis (BNF prices): EGFR M+

Regimen code		Drug acquisition (£)	Drug admin. (£)	AEs (£)	Supportive care (£)	Terminal care (£)	Total cost (£)
1	A	7459	1102	843	18,064	3531	30,998
	B	8327	1102	843	18,064	3531	29,812
3	A	5566	1722	929	18,064	3552	34,325
	B	6434	1397	929	18,064	3531	31,866
7		13,261	733	507	16,272	3531	30,355

1, DOC; 3, PAX; 7, GEF; A, combined with CIS; admin., administration; B, combined with CARB.

TABLE 75 Deterministic estimated QALYs per patient for base-case analysis (BNF prices): EGFR M+

Regimen code		Time in PFS 1	Time after PD 1	OS	QALYs in PFS 1	QALYs after PD 1	Total QALYs
1	A/B	0.5264	2.2859	2.8123	0.3338	1.0833	1.4171
3	A/B	0.5264	2.2859	2.8123	0.3338	1.0833	1.4171
7		0.9406	1.8266	2.7673	0.6226	0.8731	1.4957

1, DOC; 3, PAX; 7, GEF; A, combined with CIS; B, combined with CARB; PD, progressive disease.

range of ± 10% of the estimated value was used. The results for 20 variables which most affect the estimated ICER are shown in *Figure 40*. The most model parameters contributing most to uncertainty in the ICER are the utility model parameter values and unit costs of community health services.

The model assumes that AEs increase costs and result in disutilities for the whole duration of treatment. This is a reasonable approximation for chemotherapy, given for a limited number of cycles, but could be considered excessive for a continuous oral medication given throughout the progression-free period. To test the importance of this assumption to the estimated ICER, an additional sensitivity analysis was conducted in which the incidences of all GEF-related AEs were reduced by 50%. This resulted in a small reduction in incremental cost and a small increase in incremental QALYs gained, and reducing the base-case ICER (GEF vs PAX) from £57,440 to £53,401 per QALY gained.

TABLE 76 Epidermal growth factor receptor mutation positive

Regimen code		Drug acquisition (£)	Total cost (£)
1	A	5624	29,164
	B	5663	29,203
3	A	2661	26,908
	B	2700	26,621
7		12,302	33,366

1, DOC; 3, PAX; 7, GEF; A, combined with CIS; B, combined with CARB.

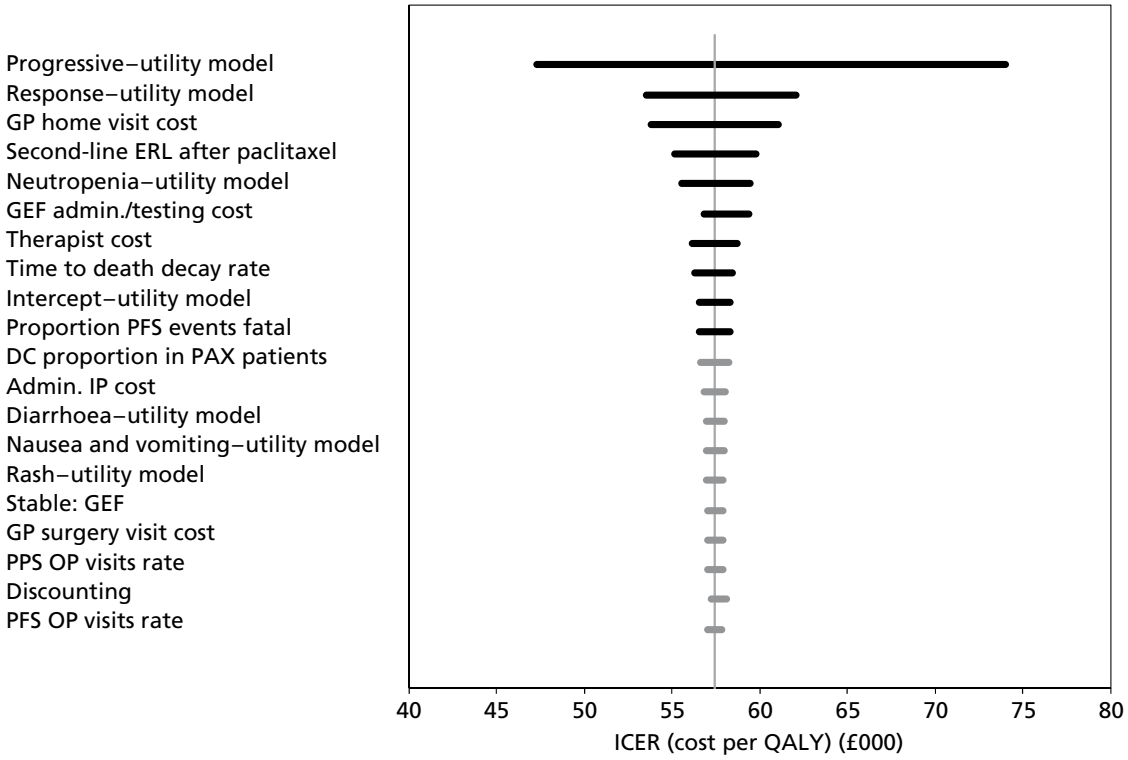

FIGURE 40 Univariate sensitivity analysis of base-case scenario with BNF prices comparison of GEF with PAX + CIS (deterministic ICER = £57,440 per QALY), showing 20 variables with the widest uncertainty range: EGFR M+. admin., administration; DC, day case; IP, inpatient; OP, outpatient.

Probabilistic sensitivity analysis

A PSA was performed for the base-case scenario including all parameters for which uncertainty could be characterised statistically. CIS was assumed as the PLAT component in chemotherapy regimens. The PSA was carried out using both BNF and eMIT prices (using CARB in place of CIS).

The summary results of both scenarios for the three treatments are shown in *Table 77*, and the cost-effectiveness acceptability plots are displayed in *Figures 41* and *42*.

Alternative scenario 1 (*British National Formulary* prices): pooling results from two trials

Summary model results for an alternative analysis based on pooling results from the two PAX trials (IPASS[15,64] and NEJGSG[63]) using BNF drug acquisition prices are shown in *Tables 78* and *79* (cost and QALYs, respectively). For PAX doublet therapy, use of CARB is associated with slightly higher costs than use of CIS. Expected survival with GEF appears to be a little better than PAX (1 month) and a corresponding benefit in terms of discounted QALYs (+0.1398). As a result, the estimated deterministic ICER for GEF vs PAX + CIS is reduced, compared with the base-case analysis, to £39,015 per QALY gained.

TABLE 77 Summary results of PSA for base-case scenarios (BNF and eMIT prices): EGFR M+

		Base case (BNF prices)		Base case (eMIT prices)	
Regimen	PSA result	Mean	Incremental	Mean	Incremental
DOC	Total cost (£)	31,184	978	29,004	2149
	Total QALYs	1.4183	0	1.4183	0
PAX	Total cost (£)	30,205	0	26,855	0
	Total QALYs	1.4183	0	1.4183	0
GEF	Total cost (£)	34,485	4280	33,341	6485
	Total QALYs	1.4956	+0.0773	1.4956	+0.0773
ICER		£55,364/QALY GEF vs PAX		£83,899/QALY GEF vs PAX	

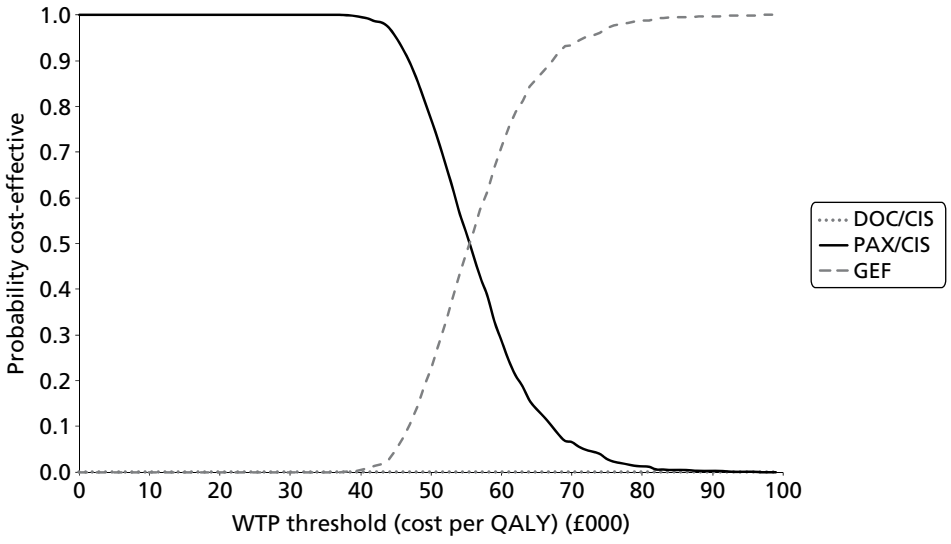

FIGURE 41 Probabalistic sensitivity analysis for base-case scenario with BNF prices, using CIS as PLAT component: EGFR M+.

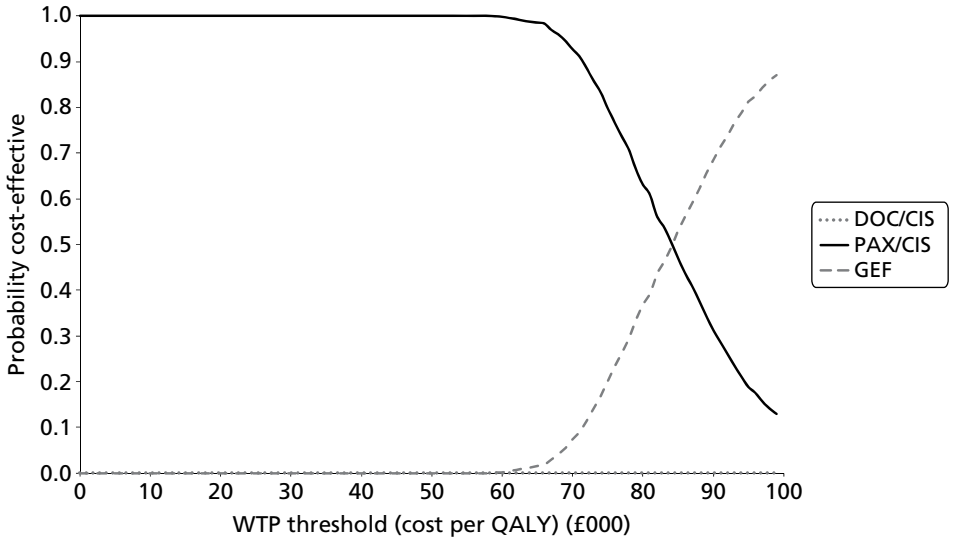

FIGURE 42 Probabalistic sensitivity analysis for base-case scenario with eMIT prices, using CARB as PLAT component: EGFR M+.

TABLE 78 Deterministic estimated cost per patient for alternative scenario 1 (BNF prices)

Regimen code		Drug acquisition (£)	Drug admin. (£)	AEs (£)	Supportive care (£)	Terminal care (£)	Total cost (£)
3	A	5559	1718	926	15,406	3627	27,236
	B	6424	1393	926	15,406	3627	32,688
7		13,193	734	493	14,656	3612	27,776

3, PAX; 7, GEF; A, combined with CIS; admin., administration; B, combined with CARB.

TABLE 79 Deterministic estimated QALYs per patient for alternative scenario 1 (BNF prices)

Regimen code		Time in PFS 1	Time after PD 1	OS	QALYs in PFS 1	QALYs after PD 1	Total QALYs
3	A/B	0.5018	1.9287	2.4305	0.3175	0.9141	1.2316
7		0.8994	1.6228	2.5222	0.5957	0.7757	1.3714

3, PAX; 7, GEF; A, combined with CIS; B, combined with CARB; PD, progressive disease.

Alternative scenario 1 (electronic market information tool prices): pooling results from two trials

Applying mean NHS negotiated prices in place of published list prices, leads to substantial reductions in acquisition costs for chemotherapy treatments, but has no other effects on costs or outcomes. Revised cost estimates are shown in *Table 80*.

Using PAX in combination with CARB now offers the minimum cost regimen for comparison with GEF. The estimated ICER for GEF compared with PAX + CARB is £54,911 per QALY gained.

Alternative scenario 2 (*British National Formulary* prices): WJTOG trial only

The summary model results for an alternative analysis based on only the WJTOG trial[65] using BNF drug acquisition prices are shown in *Tables 81* and *82* (QALYs). For DOC doublet therapy, use of CARB is

TABLE 80 Deterministic estimated cost per patient for base-case analysis using eMIT prices

Regimen code		Drug acquisition (£)	Total cost (£)
3	A	2663	24,340
	B	2702	24,054
7		12,234	31,729

3, PAX; 7, GEF; A, combined with CIS; B, combined with CARB.

TABLE 81 Deterministic estimated cost per patient for alternative scenario 1 (BNF prices)

Regimen code		Drug acquisition (£)	Drug admin. (£)	AEs (£)	Supportive care (£)	Terminal care (£)	Total cost (£)
1	A	7477	1113	852	17,627	3552	30,621
	B	8354	1113	852	17,627	3552	31,498
7		13,458	733	534	18,401	3472	36,598

1, DOC; 7, GEF; A, combined with CIS; admin., administration; B, combined with CARB.

TABLE 82 Deterministic estimated QALYs per patient for alternative scenario 1 (BNF prices)

Regimen code		Time in PFS 1	Time after PD 1	OS	QALYs in PFS 1	QALYs after PD 1	Total QALYs
1	A/B	0.6480	2.1635	2.8116	0.4116	1.0253	1.4369
7		1.0176	2.0837	3.1013	0.6736	0.9959	1.6694

1, DOC; 7, GEF; A, combined with CIS; B, combined with CARB.

associated with slightly higher costs than use of CIS. Expected survival with GEF appears to be better than PAX (3.5 months) and a corresponding benefit in terms of discounted QALYs (+0.2325). As a result, the estimated deterministic ICER for GEF vs DOC + CIS is reduced, compared with the base-case analysis, to £25,705 per QALY gained.

Alternative scenario 2 (electronic market information tool prices): WJTOG trial only

Applying mean NHS negotiated prices in place of published list prices, leads to substantial reductions in acquisition costs for chemotherapy treatments, but has no other effects on costs or outcomes. Revised cost estimates are shown in *Table 83*.

Using DOC in combination with CARB remains slightly more expensive than DOC + CIS for comparison with GEF. The estimated ICER for GEF compared with PAX + CIS is £29,553 per QALY gained.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses for all scenarios and prices yielded ICERs which were closely similar to the corresponding deterministic ICERs (*Table 84*).

TABLE 83 Deterministic estimated cost per patient for base-case analysis using eMIT prices

Regimen code		Drug acquisition (£)	Total cost (£)
1	A	5623	28,767
	B	5663	28,807
7		12,499	35,639

1, DOC; 7, GEF; A, combined with CIS; B, combined with CARB.

TABLE 84 Summary results of PSA for base-case scenarios (BNF and eMIT prices): EGFR mutation positive

Scenario	Comparator	Analysis	Estimated ICER (£)
Base case (BNF prices)	PAX + CIS	Deterministic	57,440
		Probabilistic	55,364
Base case (eMIT prices)	PAX + CARB	Deterministic	85,849
		Probabilistic	83,899
A1 (BNF prices)	PAX + CIS	Deterministic	39,015
		Probabilistic	37,749
A1 (eMIT prices)	PAX + CARB	Deterministic	54,911
		Probabilistic	55,605
A2 (BNF prices)	DOC + CIS	Deterministic	25,705
		Probabilistic	25,841
A2 (eMIT prices)	DOC + CIS	Deterministic	29,553
		Probabilistic	30,438

Summary of results for population 3 (epidermal growth factor receptor mutation positive)

The base-case analyses for GEF compared with the two chemotherapy doublets for which evidence is available show poor cost-effectiveness for GEF. Results are improved somewhat by disaggregating the three trials, but even then cost-effective ICERs (< £30,000 per QALY gained) are only obtained for the second alternative scenario based on the smallest RCT comparing GEF with the DOC + CIS doublet.

Discussion

Summary of key results

Decision analysis results for population 1 (patients with squamous disease) and population 2 (patients with non-squamous disease) consistently show VNB to be the least efficacious of the four third-generation chemotherapy agents. Although the HRs of the four treatments estimated at 12 months after randomisation appear similar, differences in long-term modelled trends, especially for OS, suggest that estimated lifetime OS is likely to be worse for VNB than for the regimens involving DOC, PAX or GEM. Moreover, VNB is consistently more expensive than the PAX options regardless of the price source used, so that VNB regimens are always dominated by other options. DOC consistently outperforms the other third-generation chemotherapy drugs primarily because of its superior long-term trend for OS. Although its long-term standardised disease risk trend is poor, this is outweighed by a favourable HR for OS at 12 months. When the more realistic NHS contract prices are considered, GEM-based regimens come into consideration alongside PAX and DOC, and CARB doublets appear preferable as a result of the less demanding administration requirements so that fewer patients need to be admitted overnight.

For population 2 (patients with non-squamous disease), PEM + CIS is clearly superior to all the third-generation chemotherapy regimens in terms of outcomes. When BNF list prices are used, PEM + CIS appears to be the most cost-effective treatment. However, when NHS-discounted contract prices for generic third-generation drugs are considered, the situation is less clear-cut, with the ICER for PEM + CIS compared with DOC exceeding £40,000 per QALY gained when assessed probabilistically.

In population 3 (patients who are EGFR M+), the trial evidence indicates that these patients have a far better prognosis than other patients with NSCLC when treated with third-generation drugs. This finding prevented the use in meta-analysis of most of the published clinical trials on patients with mixed NSCLC. Only three trials of GEF compared with either PAX or DOC doublets were found to be suitable. There was no evidence in similar populations to link PEM + CIS to the evidence network, so no economic comparison is currently possible between GEF and PEM; despite this being the most clinically relevant candidate comparator for GEF. The cost-effectiveness results are not generally favourable for GEF, which generates base-case ICERs in excess of £50,000 per QALY gained, and achieves ICERs < £30,000 per QALY only when clinical evidence is restricted to the smallest of the three RCTs.

Generalisability of results

The clinical effectiveness evidence is drawn from a comprehensive international review of RCTs undertaken to assess active systemic first-line treatments for NSCLC patients and is, therefore, of general applicability. The perspective of the economic assessment is that of the UK NHS, and draws on UK unit costs, clinical practices and guidelines to furnish model parameters. As a result, conclusions on relative cost-effectiveness may vary in other national environments.

Strengths and limitations of analysis

A novel approach to modelling trial outcomes was developed and implemented with the objective of capturing contrasting patterns of patient outcomes over time between the various treatments available. It is frequently observed that the four third-generation chemotherapy agents are considered 'clinically equivalent', but this assessment may merely mean that estimated HRs do not differ according to conventional standards. When probabilistic analysis is undertaken covering uncertainty in multiple parameters important differences in cost-effectiveness may be revealed, notwithstanding the absence of individual parameter differences normally considered significant (in this case HRs for OS and PFS). However, as there are important differences among the drugs in their mode of action, it should not be surprising that these lead to more subtle but important differences in long-term prognosis. The analysis of PFS and OS profiles for each drug pooled across all available trials indicated this to be the case, as particularly exemplified by a comparison of PEM with the third-generation drugs. Of course, this requires pooling individual trial arms and thus 'breaks randomisation'. To counter this problem, standardised profiles were developed and then conventional HRs preserving randomisation were applied to adjust the unique profiles

to represent faithfully the expected PFS and OS outcomes of each regimen. A particular strength of this method is that it avoids recourse to modelling time trends on the basis of selecting from a small number of conventional statistical parametric functions, without any obvious or explicit supporting logic.

The analysis undertaken on population 3 (patients who are EGFR M+) could not be applied to include PEM + CIS as was originally intended, owing to the lack of evidence of PEM efficacy in patients with EGFR-activating mutations. With only three modestly sized trials available and two different comparators, it was not possible to carry out any sort of indirect comparison. Therefore, the assessment is based solely on using the trial data directly – pooling all three trials for the base case and assuming equivalent effectiveness in the comparators. The results obtained are necessarily tentative, rest on limited data and are subject to question.

In particular, authors of all three trials have drawn attention to the high levels of crossover of patients randomised to chemotherapy choosing to switch to EGFR-TKI therapy on disease progression, and this is considered sufficient to explain why in none of these trials has any difference in OS been observed. However, the authors of a recent meta-analysis[141] have concluded that 'the lack of an OS benefit for initial GEF in these studies – in the overall population or even exclusively in patients with EGFR mutations – is a robust finding of this meta-analysis and apparent across all four studies'. To consider the strength of the argument for OS benefit from use of GEF obscured by high levels of crossover, a simple comparison was made of OS HRs and the proportion of chemotherapy patients switching to GEF treatment on disease progression, intended to detect a trend away from a HR of 1.0 in favour of GEF as the extent of crossover diminishes. The results (*Figure 43*) show no evidence of such a trend and, therefore, in the absence of any evidence to the contrary, the analysis shown here is based on unadjusted trial data without any alteration for crossover.

There is clearly a need for further clinical trials to be undertaken in patients with EGFR-activating mutations, which should include PEM + CIS as an important potential comparator to GEF, and should be designed to resolve the issue of crossover confounding.

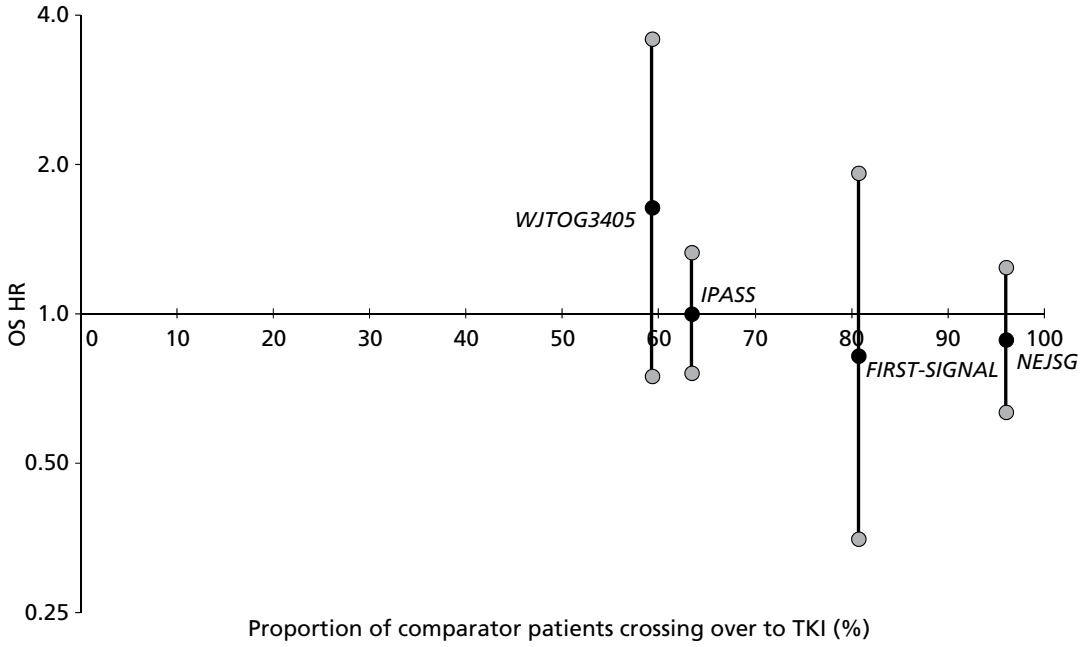

FIGURE 43 Overall survival HRs for GEF vs chemotherapy in four clinical trials compared with the extent of crossover from the chemotherapy arm to GEF on disease progression.

Chapter 5 Assessment of factors relevant to the NHS and other parties

This review highlights that histology and EGFR mutation status are important clinical factors in determining optimal chemotherapy regimens for patients and preventing the use of ineffective treatments. The recommended use of PEM and GEF require improvements in the standardisation of histology and EGFR testing within the UK. Histocytology and genetic testing need to become commonplace, standardised and routinely carried out within clinical practice in order for patients to receive optimal care. Testing for EGFR mutation status is crucial for determining which patients are eligible for EGFR-TK inhibitor drug treatment. All centres can now access EGFR mutation testing and genetic testing is becoming commonplace in the UK. However, different organisations differ in their approach to genetic testing and uptake is variable across regions, but most centres will send samples of all adenocarcinomas of lung origin to be tested for EGFR status.

There is a relatively large number of chemotherapy drugs for the first-line treatment of NSCLC that are currently being tested within Phase III trials or are filed for approval and these are shown in *Table 85*. Trials of PLAT resistance, chemotherapy in elderly patients with NSCLC and assessment of any added value of maintenance chemotherapy to first-line chemotherapy; these are all current areas of research. The proportion of squamous patients is currently decreasing in the UK and, although there are no chemotherapy agents on the immediate horizon, this is an obvious research area to explore having demonstrated different responses in patients with non-squamous NSCLC with different chemotherapy drugs.

TABLE 85 Chemotherapy drugs in Phase III development for the first-line treatment of NSCLC[a]

Drug	Possible indication	Regulatory prediction	Clinical trials	Company
Afatinib (Tomtovok®) Oral	First-line monotherapy for patients with EGFR+ mutations	EU filing expected 2012: market 2013? (Confidential)	NCT01121393 (LUX-Lung 6): single agent afatinib vs GEM + CIS for lung adenocarcinoma with tumour harbouring an EGFR-activating mutation NCT00949650 (LUX-Lung 3): single agent afatinib vs PEM + CIS for lung adenocarcinoma with tumour harbouring an EGFR-activating mutation	Boehringer Ingelheim
Cediranib (Recentin™) Oral	First-line combination therapy for advanced/metastatic disease	2016 (Confidential)	NCT00795340: cediranib plus PAX/CARB vs PAX/CARB for the treatment of advanced or metastatic NSCLC	AstraZeneca
Cetuximab (Erbitux®) i.v.	First-line combination therapy in patients with high EGFR expression	Filed in EU March 2011. Withdrawn September 2012[142] Previously filed in 2008, but CHMP issued negative opinion	NCT00112294: taxane/CARB + centuximab vs taxane/CARB as first-line treatment for patients with advanced/metastatic NSCLC NCT00148798 (FLEX): CIS/VNB + centuximab vs CIS/VNB as first-line treatment for patients with EGFR-expressing advanced NSCLC	Merck Serono
Crizotinib (Xalkori®) Oral	First-line locally advanced or metastatic; non-squamous cell NSCLC positive for *ALK* fusion gene	Likely to be filed shortly for second-/third-line treatment (already filed in US). Phase III first-line treatment study started January 2011	NCT01154140 (PROFILE 1014) crizotinib vs standard chemotherapy (PEM + CIS or CARB) in patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the *ALK* gene locus	Pfizer
ERL (Tarceva®) Oral	First-line monotherapy in EGFR mutation-positive disease	Filed in EU June 2010. 2011 – positive opinion	NCT01342965: ERL vs GEM/CIS in patients with mutations in the tyrosine kinase domain of the EGFR NCT00446225 (EUTRAC): ERL vs chemotherapy (CARB + GEM or doxetaxol/CIS) in patients with advanced NSCLC with mutations in the tyrosine kinase domain of the EGFR. This study was stopped early as it had met its primary end point	Genentech, Roche
Iniparib i.v.	First-line combination therapy in advanced (stage IV) squamous cell NSCLC	EU approval possibly third quarter 2012 (Confidential)	NCT01082549 (ECLIPSE): GEM/CARB with or without iniparib in patients with previously untreated stage IV squamous NSCLC	Sanofi-aventis
Ipilimumab (Yervoy®) i.v.	First-line combination therapy in squamous cell, stage IV or recurrent NSCLC	Unknown. Pivotal study due to complete 2015	NCT01285609: ipilimumab plus PAX/CARB vs PAX/CARB in subjects with squamous only, stage IV/recurrent NSCLC	Bristol-Myers Squibb
Motesanib Oral	First-line combination therapy in non-squamous or adenocarcinoma NSCLC	Unknown. Primary end point, OS was not achieved in MONET 1	NCT00460317 (MONET 1): motesanib + PAX/CARB vs chemotherapy alone in patients with advanced non-squamous NSCLC and in patients with adenocarcinoma histology	Takeda

ALK, anaplastic lymphoma kinase; CHMP, Committee for Medicinal Products for Human Use; MONET, Motesanib NSCLC Efficacy and Tolerability Study.

a June 2011.

Chapter 6 Conclusions

This comprehensive review is unique to the field of NSCLC research in that it compares all of the regimens currently licensed in Europe and approved by NICE for the first-line systemic treatment of patients with advanced NSCLC and is important because the future of NSCLC treatments has reached a crossroads. In summary, this review provides a basis from which to move forward, despite being limited by the published clinical effectiveness and cost-effectiveness evidence available. This review may assist clinicians to make decisions regarding the treatment of patients with advanced NSCLC as new evidence related to the important subgroups of patients becomes available in published form.

Implications for practice

The treatment of patients with NSCLC is complex. In contrast to previous research, recent clinical effectiveness evidence from RCTs demonstrates that patient health outcomes depend not only on the treatment received, but also on the characteristics of the patient population participating in the trial and of the cancer subtypes. However, in addition to the clinical evidence available, clinicians need to take the specific needs and wishes of their patients into consideration when making treatment decisions. Closer examination of clinical effectiveness and cost-effectiveness data means that we have been able to provide a comprehensive framework of information which clinicians can refer to as they attempt to balance patient factors, available treatments, treatment costs and AEs in their daily decision-making.

The results in this report relate solely to first-line systemic therapy for patients with advanced NSCLC. No inference should be drawn from them about chemotherapy in any other context. This includes adjuvant therapy, combination therapy (with radiotherapy or surgery), and second-line and maintenance therapy.

Specific treatment options

Until recently, patients with NSCLC were treated as a homogenous group; the results of previous systematic reviews concluded that, in patients with NSCLC, there were no statistically significant survival differences between DOC, PAX, GEM and VNB. This is no longer the case and increasingly trials are distinguishing between three populations of patients: patients with squamous disease, patients with non-squamous disease and patients who are EGFR M+. Our report discusses the available clinical effectiveness and cost-effectiveness evidence for agents currently approved by NICE for use in England for each of these three patient groups in turn.

However, one finding of our review and economic modelling work that applies equally to all of these patient populations is that VNB (oral or i.v.) is less effective and more costly than at least one of the other options (DOC, PAX and GEM) and, therefore, is not shown to be cost-effective under any circumstances. Clearly, this finding will be of concern to those clinicians who currently favour the use of this treatment.

Given the recent changes in chemotherapy costs (that is the decrease in costs as drugs come off patent) other factors begin to enter into the decision-making process. One important issue identified by this review is the effect these changes may have on the choice of use of the PLAT component of chemotherapy doublet regimens. The use of CIS is more likely than CARB to require an overnight stay in hospital, and with reducing drug costs, additional administration costs begin to impact significantly on the overall cost-effectiveness of the various treatment options, and may potentially lead to greater use of CARB administered in a day-case setting.

Patients with squamous disease

Our report shows that for patients with squamous disease, there is no statistically significant difference in terms of OS between DOC, PAX, GEM and VNB. However, our analyses demonstrate that there are slight

differences between these treatments in terms of clinical effectiveness and when these differences are modelled over the longer term (>12 months) and the costs of the treatments are taken into consideration, then differences in cost-effectiveness begin to appear. For this group of patients, PAX is shown to be the preferred option when the WTP threshold is low. As the WTP threshold is increased GEM and DOC can be considered cost-effective treatments, so that at high WTP thresholds DOC becomes the preferred option.

Patients with non-squamous disease

In terms of OS, the clinical evidence shows that PEM is the preferred option for this group of patients, showing a statistically significant gain in OS over all of the third-generation doublet regimens. For cost-effectiveness, a similar pattern of ranking applies as was found for treatment of patients with squamous disease (PAX→GEM→DOC); however, with PEM added as the final 'most effective but most costly' option a high WTP threshold (up to £50,000 per QALY) is required in order for PEM to be considered acceptable. If and when the acquisition cost of PEM is reduced, the case for its wider use will be strengthened.

Patients who are epidermal growth factor receptor mutation positive

Patients with EGFR M+ status are a small subgroup of patients with NSCLC who have predominantly non-squamous disease. Trial evidence indicates that this patient population has a far better clinical prognosis than other patients with NSCLC. However, it is difficult to identify optimal treatments for this group of patients as the available trial evidence indicates that there is a PFS benefit for patients associated with GEF, but that there is no statistically significant OS benefit associated with GEF compared with DOC or PAX. Decision analysis based on the three GEF trials[15,63–65] currently published suggests high ICERs when comparing GEF to third-generation chemotherapy doublets (PAX and DOC), greater than would normally be considered acceptable in the UK. The absence of any direct evidence of PEM effectiveness in the small EGFR M+ subgroup currently precludes any comparison between GEF and PEM.

Research recommendations

Future trials of first-line treatments for patients with NSCLC will need to take into consideration many more factors than has historically been the case. NSCLC is no longer considered as a single disease entity and the design of future lung cancer trials needs to reflect the influence of factors such as histology, genetics and any new prognostic biomarkers that are currently being identified. In addition, trials will need to be adequately powered so as to be able to test for statistically significant clinical effectiveness differences within patient populations.

Current standard treatment for patients with advanced and metastatic NSCLC is first-line chemotherapy; second- and third-line treatments are also available for those patients who are fit enough. As more patients become eligible for second- and third-line treatments, more consideration has to be given to the design of trials and how OS can be appropriately measured. Flexibility is required to design trials which not only permit patients to cross over to other treatments but also to design trials where the survival data collected can be meaningfully interpreted. For example, this may lead to more trials being designed with designated sequencing of treatments. It is acknowledged that such trials are unlikely to be funded by the pharmaceutical industry where demonstration of PFS is the accepted marker for obtaining market authorisation.

However, there are other gaps in our knowledge about current treatments and outcomes for patients with NSCLC. The results in this report are based entirely on the analysis of published data from Phase II and Phase III clinical trials. It is well known that patients in such trials are not necessarily representative of patients seen in UK clinical practice. New initiatives to collect data on UK patients and the treatment they receive are now in place through the emergence of the National Cancer Intelligence Network.[87] The National SACT data set became operational on the 1 April 2012 and will provide this detailed information. It will also be feasible to include health economic data into such future analyses. We would strongly

endorse the development of initiatives of this kind in the effort to provide data that can more accurately define the true cost–benefit ratio of treatment interventions in this patient population.

A major gap in the literature that has been identified by this review is the lack of published HRQoL data in this patient population in a clinical trial setting. Results of recent research have shown that it is possible to collect reliable HRQoL data in cancer patients during treatment. As clinicians consider the AE profiles of treatments and subsequent effects on HRQoL in their decision-making, all trials should include mechanisms to elicit and report good-quality HRQoL data reflecting patients' experiences of their treatment during trials.

Concluding remarks

The completion of this review has taken a significant length of time and during that period there has been explicit acknowledgement in the published literature of the important differences in the characteristics of patients who previously were identified as having NSCLC. It is anticipated that no further RCTs will be carried out involving patients with NSCLC as a homogeneous group, but that consideration of the important patient subgroups will take precedence and allow for the development of more specialised and targeted treatments which, in turn, will require RCTs of increasingly sophisticated design.

This report offers clinicians informed evidence about all aspects of currently available treatments for patients with lung cancer. Clearly, health-care professionals make daily decisions about what is best for their patients. For instance, individual side-effect profiles may mean that a particular drug is selected that might be assessed as less cost-effective but better suit a particular patient's preference (e.g. the use of alternative drugs to DOC where high-dose steroids, hair loss or neurological side effects need to be avoided). In this context, the short OS gain and significant symptoms experienced by patients with advanced NSCLC need to be considered. However, health-care professionals are also tasked with making difficult decisions with populations in mind and it is hoped that this report will provide up-to-date information that will support clinicians in their discussion with patients regarding the benefits of the various treatment options.

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Appendix 1 Details of clinical search strategies

Ovid MEDLINE(R) 1990 to March week 3 2009

		Results
1	randomized controlled trial.pt.	266,601
2	controlled clinical trial.pt.	78,726
3	randomized.ab.	177,144
4	placebo.ab.	110,573
5	randomly.ab.	128,581
6	trial.ab.	184,266
7	or/1-6	579,686
8	(animals not (humans and animals)).sh.	3,254,838
9	7 not 8	525,513
10	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	18,909
11	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18,385
12	10 or 11	22,812
13	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	182,017
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	254,221
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20,673
16	or/13-15	355,832
17	9 and 12 and 16	3045
18	limit 17 to (english language and yr="1990 - 2009")	2594

EMBASE 1990 to 2009 week 13

		Results
1	Randomized Controlled Trial/	167,319
2	randomized.ab.	171,365
3	placebo.ab.	106,176
4	randomly.ab.	114,323
5	trial.ab.	168,003
6	controlled clinical trial.pt.	0
7	Controlled Clinical Trial/	58,798
8	or/1-7	464,615

		Results
9	limit 8 to human	396,769
10	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18,740
11	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	22,601
12	10 or 11	25,216
13	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	128,596
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	220,301
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20,371
16	exp Cancer Radiotherapy/ or exp Chemotherapy/	225,579
17	or/13-16	386,860
18	9 and 12 and 17	3521
19	limit 18 to (english language and yr="1990 - 2009")	3034

The Cochrane Library (Issue 3 of 4, July 2010)

"non small cell lung cancer in Title, Abstract or Keywords and (vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab or Vindesine or Docetaxel or Cisplatin or Etoposide or Paclitaxel or Carboplatin or Navelbine) in Title, Abstract or Keywords in Cochrane Methodology Register"

Cochrane Central Register of Controlled Trials = 1716.

Appendix 2 Protocol

1. Title of project

Clinical and cost effectiveness of first-line therapy for adult patients with non-small cell lung cancer

2. TAR team

Liverpool Reviews and Implementation Group (LRiG), University of Liverpool

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For details of expertise within the TAR team see section 8.

3. Plain English summary

Non-small cell lung cancer (NSCLC) is a disease that affects almost 40,000 people in the UK each year. The treatment of the disease is hampered by its late diagnosis and very poor response to therapy and subsequently poor patient survival. In 2005 the National Institute for Health and Clinical Excellence (NICE) conducted a technology appraisal that evaluated the effectiveness of a number of drug therapies used to treat the disease. Over the past three to four years NICE has individually appraised a number of new drug treatments and made recommendations for treatment. These treatments have not been examined as a group or compared to each other. This proposal provides a protocol for a systematic review that will bring together the evidence related to the clinical effectiveness of these newer treatments, compared to those recommended in previous reviews as well as providing a re-examination of the cost effectiveness of the newer drug therapies.

4. Background

The most recent comprehensive review of chemotherapy treatment of NSCLC was conducted by Clegg *et al.* in 2002[1] and was integral to the development of the NICE guidelines for the diagnosis and treatment of NSCLC in 2005.[2]

In 2005 the NICE Single Technology Appraisal (STA) process was introduced with the purpose of appraising technologies close to their date of launch to ensure the availability of appropriate technologies within the

NHS as soon as possible. The design of the STA process means that each appraisal examines the use of a single technology for a single clinical indication. As a result, it is possible for several single technologies to be appraised for the same condition over a period of time with no formal link between the appraisals. NSCLC is an example of this and at least four STAs have been proposed or conducted regarding first-line chemotherapy treatments for patients with non-small cell lung cancer (NSCLC) since the inception of the STA process and since the previous comprehensive review of lung cancer treatments conducted by Clegg et al in 2002.[1] In fact the current NICE website lists a total of 13 appraisals that examine the treatment of NSCLC. These are a mix of first- and second- line treatment and comprise appraisals that are complete, have been terminated, delayed or are proposed.[3]

NICE is currently in the process of updating the guidelines related to the diagnosis and treatment of lung cancer.[4] LRiG has been in touch with the former head of the NICE clinical guidelines programme, Dr Fergus MacBeth, who has indicated that a comprehensive review of first-line therapy for NSCLC will not be undertaken as a part of this guideline process but that such a review would complement existing research in this area and that the availability of an up-to-date economic model would add great value. LRiG has contacted Andrew Champion (NCC manager) and Mia Schmidt-Hansen (systematic reviewer working on the update) who confirmed that the update will not include chemotherapy alone because there are so many NICE appraisals being done in the area. The guidelines group are however updating the review on chemoradiation. There are also indications that an updated Cochrane review is due to come out in mid-April 2010 which reviews chemoradiotherapy versus radiotherapy alone and also concurrent versus sequential chemoradiotherapy.

The Liverpool Reviews and Implementation Group (LRiG) has carried out a number of STAs in the area of NSCLC and believes that there is now a need to bring together the disparate clinical and cost effectiveness evidence for first-line treatment of NSCLC in the form of a comprehensive Health Technology Assessment report. We believe that an independent HTA report on chemotherapy and radical chemoradiotherapy for NSCLC will be very useful and will inform both current and future guidelines. This proposed review will assist policy makers in deciding how the newer NSCLC chemotherapy agents (e.g. pemetrexed) fit into the treatment pathway in the NHS in England and Wales.

This document describes the protocol for such a report and is being submitted for consideration as a part of LRiG's current TAR research contract. A decision was taken by LRiG regarding the importance of this project and therefore work on the clinical component of the project has already begun (see timelines below.)

5. Decision problem

Background

Currently, NICE guidelines[2] recommend that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status to improve survival, disease control and quality of life. This should consist of a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin). Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation agent. NICE also recommends that pemetrexed in combination with cisplatin may also be considered as a first-line therapy for patients with locally advanced or metastatic NSCLC who are confirmed as having large cell or adenocarcinoma histology; NICE has three other appraisals in its STA workplan.[5]

The current Scottish Intercollegiate Guidelines Network (SIGN) guideline states that chemotherapy with a platinum-based combination doublet regimen should be considered in all stage IIIB and IV NSCLC patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive chemotherapy. It further states that in these patients, the number of chemotherapy cycles given should not exceed four. No particular chemotherapy doublet or platinum agent is recommended in the guideline.[6]

The European Society for Medical Oncology (ESMO)[7] has published clinical recommendations for the diagnosis, treatment and follow-up of NSCLC. The recommendation for the treatment of stage IV disease states that 'Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms' (p 40).

Epidemiology

Lung cancer is the leading cause of death worldwide, while NSCLC accounts for approximately 80% of all lung cancers diagnosed.[8] The LUCADA database lists the main sub-types of NSCLC as squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (NSCLC-NOS).[9]

Over 38,000 people in the England and Wales were diagnosed with lung cancer in 2005 making it the second most commonly diagnosed cancer, after breast cancer, equivalent to more than 100 people per day being diagnosed with lung cancer. The link between smoking and lung cancer is well established: approximately 90% of lung cancer is the result of exposure to tobacco smoke. The link between smoking and poverty has also been proven; making lung cancer a disease that disproportionately affects people in the lowest socio-economic groups.[9,10] Survival from lung cancer is poor. Lung cancer was responsible for approximately 34,000 deaths in 2006 and is the most common cause of cancer death in the UK, accounting for more than one-in-five. Only 7% of lung cancer patients survive over five years after diagnosis.[10]

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages – about two-thirds of patients are not diagnosed until it has reached advanced stages of the disease and is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anticancer treatment rates.[10]

The technology

As outlined above there are several different first-line chemotherapy agents available to patients with NSCLC. In summary, chemotherapy treatments recommended by NICE include platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine; more recently, pemetrexed in combination with cisplatin has also been recommended by NICE for patients with large cell or adenocarcinoma.[2]

In addition, there are a variety of first-line chemotherapy treatments which have been approved by the European Medicines Agency (EMA) for patients with NSCLC that have not yet been appraised by NICE including gefitinib, cetuximab, bevacizumab and erlotinib.[3]

In addition, best supportive care (BSC) and different types of chemo-radiation are also first-line treatments that are available to patients with NSCLC. Current guidelines state that: 'Patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy should be offered sequential chemoradiotherapy' (p. 8).[2]

Objectives of the HTA project

The objectives of the project are to evaluate the clinical and cost effectiveness of first-line therapy for adult patients with locally advanced or metastatic NSCLC.

6. Methods for synthesising clinical effectiveness evidence

Systematic review search strategy – published studies

The following databases will be searched for relevant published literature for the period 1990 to September 2009:

- EMBASE
- MEDLINE
- The Cochrane Library (which includes DARE, HTA and NHS EED).

Searches have been limited to these databases based on the evidence related to searching presented by Royle et al.[11] Details of the search strategies used to explore EMBASE and MEDLINE are available in Appendix A. An update search will be carried out in 2010 to capture trials published during the production of this review.

Where electronic search facilities are available, the conference reports of organisations such as the American Society for Clinical Oncology (ASCO) will be searched for details of conferences and abstracts to identify any relevant studies and if data are available, these will be considered for inclusion in the review.

Bibliographies of previous reviews identified by the search (e.g. Clegg *et al*. 2001[1]) and retrieved articles will be searched for further studies. The NICE website will be searched to identify manufacturers' submissions in this treatment area.

Clinical and statistical reviews of relevant chemotherapy treatments will be sought from the US Food and Drug Administration and the EMEA website will be examined to identify further trial information.

A database of relevant references will be developed using EndNote X3 software package.

Study selection

The citations identified by the search strategy will be assessed for inclusion through two stages. Firstly, two reviewers will independently screen all of relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Secondly, full text copies of these potentially relevant studies will be obtained and assessed independently by two reviewers using the inclusion and exclusion criteria outlined below (Table 1). Any disagreements between reviewers will be resolved by discussion at each stage and, if necessary, a third reviewer will be consulted.

Studies that do not meet all of the inclusion criteria will be excluded and their bibliographic details listed with reasons for exclusion. Ongoing studies that do not report relevant outcomes but meet the inclusion criteria will be listed for future use. In the event that data from randomised controlled trials (RCTs) are missing or limited, data from non-randomised studies may be used. The identification and use of such data will be described in the final report.

Inclusion criteria

TABLE 1 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials Systematic reviews of randomised controlled trials
Patient population	Chemotherapy naïve adult patients with locally advanced or metastatic non-small cell lung cancer
Interventions	Any first-line chemotherapy treatment currently licensed including: Platinum-based chemotherapy (carboplatin or cisplatin) in combination with docetaxel, gemcitabine, paclitaxel, vinorelbine or bevacizumab Pemetrexed plus cisplatin Single agent therapies including erlotinib, gefitinib and cetuximab Any first-line chemo-radiation therapy
Comparators	It is envisaged that the interventions will be compared with active therapy as described above or best supportive care Comparisons of variation in dosing, timing (including concurrent or sequential) or mode of treatment regimens will also be included even when the intervention and comparator drug are the same
Outcomes	Primary outcomes: Overall survival or Progression free survival Secondary outcomes Response rates Adverse effects Health related quality of life
Other considerations	Only studies published since 1990 in full and with English-language abstract will be included

Data extraction

Data from the included studies will be extracted as detailed below and will include the information listed in Appendix B.

Data relating to population characteristics, study design and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on data extraction forms which will be piloted using a sample of included studies. Time permitting, authors and/or sponsors of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed in the report.

Quality assessment

All included studies, will be assessed for methodological quality. The quality of RCTs will be assessed using criteria based on CRD Report No. 4[11] (see Appendix C). Questions 4 and 5 will be adapted to reflect the characteristics of patients with NSCLC.

Data relating to quality assessment will be extracted by one reviewer and independently checked for accuracy by a second reviewer and any disagreements will be discussed; a third reviewer will be consulted, if necessary, to achieve consensus.

Methods of analysis/synthesis

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. The possible effects of study quality on the clinical effectiveness data and review findings will be discussed. Where there are sufficient data, and it is appropriate to do so, meta-analyses will be

performed using the Mantel-Haenszel methodology for a fixed-effect model. The meta-analysis will be carried out using the statistical package Review Manager 4.2. Treatment effects will be presented as weighted mean differences for continuous data.

Heterogeneity between trial results will be tested using a standard chi-squared test, with a threshold value of $p < 0.1$, and with the I^2 statistic.[12] Where quantitative heterogeneity is indicated, analysis using a random-effects model will be conducted for comparison with results of fixed-effect analysis to assess the robustness of the model chosen. The DerSimonian and Laird methodology will be used for the random effects model.[13] Heterogeneity between the included studies will be assessed by considering differences in (a) the study population (b) intervention (c) outcome measures and (d) study quality.

For binary outcomes (dichotomous data), where sufficient data are available, relative treatment effects will be presented in the form of odds ratios (OR) and/or relative risks (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used, the standardised mean difference (SMD) will be calculated provided skewness is not too great. For time to event outcomes, log hazard ratios (log HR) will be presented. Data will be pooled only if it is clinically and statistically relevant to do so.

Subgroup analyses will be conducted according to the type of disease (e.g. non-squamous, EGFR+ ect) and age of patients if suitable data are available.

7. Methods for synthesising cost effectiveness evidence

Systematic review of published economic literature – search strategy

The search strategy described in section 6 will be used to identify studies examining the cost effectiveness of first-line chemotherapy for adult patients with NSCLC. The search strategy is designed to meet the primary objective of identifying economic evaluations for inclusion in the cost-effectiveness literature review. At the same time, the search strategy will be used to identify economic evaluations and other information sources which may include data that can be used to populate a de novo economic model where appropriate. Searching will be undertaken in MEDLINE and EMBASE as well as in the Cochrane Library, which includes the NHS Economic Evaluation Database (NHS EED). The dates for the searches will be from 1990 September 2009.

Study selection

Titles and abstracts will be examined for inclusion by two reviewers independently. Potentially relevant studies will then be obtained in full text and examined more carefully by two independent reviewers using the economic inclusion criteria outlined in Table 2. Any disagreement will be resolved by consensus, and if necessary a third reviewer will be consulted. Only full economic evaluations (assessing both outcomes and benefits) will be included. However, to supplement findings, additional information on costs and benefits will be collated and discussed in narrative format as appropriate.

Inclusion criteria

TABLE 2 Inclusion criteria (cost effectiveness)

Study design	Full economic evaluations that consider both costs and consequences (cost-effectiveness analysis, cost-utility analysis, cost minimisation analysis and cost benefit analysis)
Outcomes	Incremental cost per life year gained Incremental cost per quality adjusted life year gained

Data extraction

Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables and will include, but not be limited to, the criteria set out in Appendix D.[4] Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

Quality assessment

The quality of the individual cost-effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the included studies will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and colleagues[4] (see Appendix D). This checklist reflects the criteria used to assess the quality of published economic evaluations as detailed in the methodological guidance developed by the NICE.[12] The information will be tabulated and summarised within the text of the report.

Methods of analysis/synthesis

(i) Cost-effectiveness review of published literature

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

(ii) Development of a de novo economic model

If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of first-line chemotherapy treatments for patients with NSCLC. Where possible, the results will be presented as incremental cost per quality adjusted life year (QALY) ratios.

Methods for estimating costs, benefits and cost effectiveness ratios in the de novo economic model

a. Cost data

The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with the interventions. If evidence indicates that a societal perspective is required to credibly value all important costs and outcomes, this will be explored and presented in the sensitivity analysis. The relevant time horizon of analysis will be a patient's lifetime in order to reflect the chronic nature of the disease.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate costs will be discounted at 3.5% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[12]

b. Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. LRiG anticipates that the main measures of benefit will be increased QALYs.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[12]

c. Modelling

LRiG's ability to construct an economic model will depend on the data available. Where modelling is appropriate, a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis (see Section d below) will be presented. In addition, LRiG will provide an assessment of the model's strengths and weaknesses and discuss the implications of using different assumptions in the model. The time horizon will be a patient's lifetime. Both costs and QALYs will be discounted at 3.5% as recommended by NICE.[12]

A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical-effectiveness review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost-effectiveness analysis or cost-minimisation analysis will be undertaken.

d. Sensitivity analysis

If appropriate, sensitivity analysis will be applied to LRiG's model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

If evidence indicates that a societal perspective is required to value credibly all important costs and outcomes, this will be explored and presented.

8. Expertise in this TAR team

The Liverpool Reviews and Implementation Group (LRiG) was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance is to conduct Technology Assessment Reviews commissioned by the HTA programme. The team has substantial expertise in systematic reviewing, literature searching, assessing clinical outcomes, economic modelling and health economics, and is well practised in applying this expertise to health technology evaluations. In addition, various members of the team have been involved in recent STA appraisals in the area of NSCLC.

A subset of the LRiG team and local clinicians* have been selected on the basis of the specific expertise they bring to the project to work on this project (Table 3).

TABLE 3 LRiG team and expertise

Team member	Expertise	Contribution
Professor Adrian Bagust	Senior economic modeller	Economic modelling
Angela Boland	Health economics and systematic reviewing	Systematic review of economic evaluation/economic modelling
Tamara Brown	Systematic reviewing	Lead reviewer responsible for project management and systematic review of the clinical effectiveness data including meta-analyses
Ms Rumona Dickson Director of LRiG	Assessing clinical outcomes, systematic reviewing	Input into all aspects of the clinical component of the review
Yenal Dundar	Information specialist, assessing clinical outcomes	Development of the search strategies and input into the clinical components of the review
Emer McKenna*	Clinical/oncology expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
James Oyee	Medical statistician	Assessment of medical statistics
Libby Richards*	Clinical/cancer treatment expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
Carlos Saborido-Martin	Economic modelling	Economic modelling

9. Timetable/milestones

The previous involvement of the LRiG team in the appraisal of a variety of treatments for NSCLC within the STA process brought the LRiG team to the conclusion that there was a need for a full systematic review in this area. LRiG therefore identified local clinicians that were interested in the project and began work on the clinical component of this review during periods when other NICE projects were put on hold or cancelled. Work on this review has therefore begun but has been slow to move forward as other NICE and HTA work took priority. We are now proposing that this work be incorporated into our contracted TAR units for this and the coming year. Timelines for progression of the project are dependent on reviewer feedback and a decision regarding the appropriateness of including the work within our contract. Dates for completion therefore will be negotiated when these other decisions are taken.

Dates (estimated)	Activity
Internally done in January, 2009	Finalisation of protocol
Initial screening began in February, 2009	Screening of titles and abstracts
Completed January 2010	Inclusion/exclusion of full text papers
Commenced July 2009	Data extraction (clinical)
Commenced July 2009	Quality assessment (clinical)
TBC – not yet commenced	Data extraction (cost effectiveness)
TBC - not yet commenced	Quality assessment (cost effectiveness)
TBC - not yet commenced	Data synthesis and economic modelling
TBC	Draft report available for internal peer review
Depending on final HTA approval Provisionally December 2010	Full report submitted

10. Potential peer reviewers

Dr Noelle O'Rourke (Consultant Clinical Oncologist)

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11. References

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12. Appendices

Appendix A: Details of clinical search strategies

Ovid MEDLINE(R) 1990 to March Week 3 2009

		Results
1	randomized controlled trial.pt.	266601
2	controlled clinical trial.pt.	78726
3	randomized.ab.	177144
4	placebo.ab.	110573
5	randomly.ab.	128581
6	trial.ab.	184266
7	or/1-6	579686
8	(animals not (humans and animals)).sh.	3254838
9	7 not 8	525513
10	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	18909
11	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18385
12	10 or 11	22812
13	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	182017
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	254221
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20673
16	or/13-15	355832
17	9 and 12 and 16	3045
18	limit 17 to (english language and yr="1990 - 2009")	2594

EMBASE 1990 to 2009 Week 13

		Results
1	Randomized Controlled Trial/	167319
2	randomized.ab.	171365
3	placebo.ab.	106176
4	randomly.ab.	114323
5	trial.ab.	168003
6	controlled clinical trial.pt.	0
7	Controlled Clinical Trial/	58798
8	or/1-7	464615
9	limit 8 to human	396769

		Results
10	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18740
11	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	22601
12	10 or 11	25216
13	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	128596
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	220301
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20371
16	exp Cancer Radiotherapy/ or exp Chemotherapy/	225579
17	or/13-16	386860
18	9 and 12 and 17	3521
19	limit 18 to (english language and yr="1990 - 2009")	3034

Appendix B: Details of clinical data extraction

Data extraction will include but may not be limited to:

Study details

- Author/Year/Endnote reference
- Randomisation
- Recruitment
- Funding
- Country
- Power
- Setting
- Population
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Intention to treat analysis done?
- Length of follow-up

Intervention details

- Intervention (i.e. drug name(s) and details)
- Dose of intervention
- Duration of intervention

Participant characteristics

- Number of participants randomised
- Number of participants assessed for primary outcome
- Age
- Sex
- Performance status
- Disease stage
- Were baseline demographics and disease state comparable?

Outcomes

- Overall survival
- Median survival time
- Survival rate

- Progression free survival
- Tumour response rate
- Duration of response
- Quality of life
- Haematological toxicity
- Non-haematological toxicity
- Toxic death

Appendix C: Details of clinical quality assessment

The quality of RCTs will be assessed using criteria based on CRD Report No. 4[13]

1. Was the method used to assign participants to the treatment groups really random?*
2. Was the allocation of treatment concealed?**
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Is there any evidence to suggest that the authors measured more outcomes than they reported?
15. Was an intention to treat analysis included?

*(Computer-generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)

**(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially-numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).

Items will be graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/ partially (item partially addressed), **?** unclear or not enough information, or **NA** not applicable

Appendix D: Details of economic data extraction and quality assessment

Cost effectiveness data extraction will include, but not be limited to:

- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study
- Cost items
- Cost data sources

- Country, currency year
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models
- Cost-effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

Studies of cost effectiveness will be assessed for quality using the following criteria, which is an updated version of the checklist developed by Drummond:[4]

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results

Appendix 3 Details of clinical data abstraction

Study details

- Author/year/EndNote reference.
- Randomisation.
- Recruitment.
- Funding.
- Country.
- Power.
- Setting.
- Population.
- Inclusion/exclusion criteria.
- ITT analysis.
- Length of follow-up.

Intervention details

- Intervention.
- Dose of intervention.
- Duration of intervention.

Participant characteristics

- Number of participants randomised.
- Number of participants assessed for primary outcome.
- Age.
- Sex.
- PS.
- Disease stage.
- Baseline demographics and disease state.

Outcomes

- OS.
- Median survival time.
- Survival rate.
- Progression-free survival.
- Tumour response rate.
- Quality of life.
- Haematological toxicity.
- Non-haematological toxicity.
- Toxic death.

Appendix 4 Details of clinical quality assessment

The quality of RCTs will be assessed using CRD's criteria:

- Was the method used to assign participants to the treatment groups really random?[a]
- Was the allocation of treatment concealed?[b]
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and PS?
- Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and PS?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for withdrawals stated?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Was an ITT analysis included?

a Computer-generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week.

b Concealment will be deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered identical containers, on-site computer-based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque.

Items will be graded in terms of: ✓, yes (item properly addressed); ✗, no (item not properly addressed); ✓/✗, partially (item partially addressed); ?, unclear/not enough information; or NA, not applicable.

Appendix 5 Letter to authors of included studies (via e-mail)

Dear Professor

We are writing to request hazard ratio data from one of your lung cancer trials (see below) in order to include your trials in our systematic review entitled: Details of our project can be found at http://www.hta.ac.uk/2238.

Our research group, the Liverpool Reviews and Implementation Group (LRiG), is funded through the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme in the UK. LRiG was originally established in 1999 to conduct systematic reviews of clinical and cost effectiveness evidence commissioned for the National Institute for Health and Clinical Excellence (NICE).

In 2005 NICE conducted a technology appraisal that evaluated the clinical effectiveness of a number of drug therapies used to treat patients with NSCLC[1]. Since then, NICE has individually appraised and recommended a number of new treatments; these treatments have not yet been examined as a group or compared to each other. Our systematic review brings together the published evidence related to the clinical effectiveness of both older and newer treatments, and, in addition, provides a re-examination of the cost-effectiveness evidence available.

To ensure completeness of our systematic review we would like to include your trial detailed below in our meta-analysis, however additional data are required from you on hazard ratios for overall survival (OS) and progression free survival (PFS).

Please could you complete the details in the table below and email back to me? We would be grateful for any information you can provide, and we will acknowledge these data in our report. Please do not hesitate to contact me if you require further information. Thank you for your time.

Kind regards

Tamara Brown (Project Lead and Clinical Research Fellow)

1 National Institute for Health and Clinical Excellence. CG24: Lung cancer: full guidelines. London: NICE; 2005 [cited 2009 Sept]; Available from: http://guidance.nice.org.uk/CG/Wave17/23.

Title	Hazard ratio for overall survival (OS)	95% confidence intervals for OS	Hazard ratio for progression free survival (PFS)	95% confidence intervals for PFS

Appendix 6 Code from the Multi-parameter Evidence Synthesis Research Group

```
model{
#Model for log-hazard ratios
for(i in 1:ndp){
        prec[i]<- 1/(se[i]*se[i])
        lhr[i]~dnorm(delta[i],prec[i])

#Random effects model for log hazard ratios
                delta[i] ~ dnorm(md[i],taud[i])
                taud[i] <- tau * (1 + equals(arm[i],3) /3)
                md[i] <- d[t[i]] - d[b[i]] + equals(arm[i],3) * sw[i]

#Calculation of residual deviance
        rhat[i] <- lhr[i] * prec[i]
        dev[i] <- (lhr[i] - delta[i])*(lhr[i] - delta[i])/(se[i]*se[i])
        }
        resdev <- sum(dev[])

# Adjustment for multi-arm trials
        sw[1]<- 0
        for (i in 2:ndp) { sw[i] <- (delta[i-1] - d[t[i-1]] + d[b[i-1]])/2}

#Non-informative priors for log hazard ratios
        d[1]<-0
        for (k in 2:nt){
        d[k] ~ dnorm(0,.00001) # vague priors for basic parameters

        }

        sd~dunif(0,100)
        tau<-1/pow(sd,2)

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:nt){
        rk[k]<- rank(d[],k)

        best[k]<-equals(rk[k],1)
        }

#All pair-wise log hazard ratios and hazard ratios
for (c in 1:nt-1){
        for (k in (c+1):nt){
                lhzr[c,k] <- d[k] - d[c]
                HR[c,k] <- exp(lhzr[c,k])
                }
        }

}
```

Appendix 7 References of excluded clinical studies with reasons for exclusion

Reference	Reason for exclusion
Fisher 2000[143]	Short report
Georgoulias 2003[144]	Interim analysis on incomplete patient sample
Gridelli 2008[145]	No outcome data – rationale and protocol only
Gridelli 2007[146]	Rofecoxib (withdrawn)
Grigorescu 2002[147]	Quasi-randomised
Leong 2003[148]	Amifostine (Ethyol®, LABORATOIRES Genopharm) (cytoprotective adjuvant; indication for NSCLC withdrawn 2005)
Miller 2003[149]	Dosing study using sequentially enrolled cohorts
O'Brien 2004[150]	PLAT-based chemotherapy with or without SRL172 (killed *Mycobacterium vaccae* suspension)
Ramalingam 2006[151]	Subanalysis by age
Vansteenkiste 2003[152]	Detailed individual symptom control analysis, influence of CIS use, age, PS and duration of treatment
[a]Gao 2005[153]	Unclear if patients had previous chemotherapy
[a]Lin 2002[154]	Not a RCT
[a]Liu 2006[155]	Unclear if patients had previous chemotherapy
Semrau 2003[156]	No English abstract
[a]Teng 2003[157]	Not a RCT
[a]Xu 2006[158]	Does not report survival data
[a]Zhang 2008[159]	Unclear if patients had previous chemotherapy

a Translated.

Appendix 8 Trial characteristics

Trial	Aim	Phase	Funding	Multicentre?	International?	Country	Sufficiently powered?	Follow-up (months)
Kelly 2001[48]	To determine whether or not PAX + CARB offered a survival advantage over VNB + CIS	III	Public Health Service Cooperative Agreement grants (National Cancer Institute), Glaxo Wellcome Inc., Bristol-Meyers Squibb	Yes	No	USA	Yes	24
Scagliotti 2002[43]	To evaluate whether GEM + CIS or PAX + CARB offer any advantage over VNB + CIS	III	Eli Lilly and Company	Yes	No	Italy	Yes	24
Schiller 2002[47]	To determine whether CIS + GEM, CIS + DOC or CARB + PAX are superior to CIS + PAX	Unclear	National Institutes of Health	Yes	No	USA	Yes	24
Fossella 2003[44]	To investigate whether or not DOC + PLAT regimens improve survival and affect QoL compared with VNB + CIS	III	Aventis Pharma	Yes	Yes	Australia, Canada, Europe, Israel, Latin America, Lebanon, New Zealand, South Africa and the USA	Yes	24
Gebbia 2003[49]	To compare VNB + CIS with GEM + CIS, and to sequential chemotherapy with GEM + IFOS followed by VNB + CIS or VNB + CIS followed by GEM + IFOS	III	NR	Yes	No	Italy	No	12
Gridelli 2003[45]	To assess whether or not GEM + VNB had QoL benefits without influencing negatively on survival, compared with GEM + CIS and VNB + CIS	III	Clinical Trials Promoting Group Italy, Eli Lilly and Company, Canada; Associazione Italiana per la Ricerca sul Cancro	Yes	Yes	Canada and Italy	Yes	12
Smit 2003[46]	To compare efficacy of PAX + CIS vs GEM + CIS and PAX + GEM	III	National Cancer Institute	Yes	Yes	Belgium, Egypt, Germany, Netherlands and Spain	Yes	12
Chen 2004[51]	To evaluate the efficacy of weekly PAX + CIS vs VNB + CIS	II	NR	No	No	Taiwan	Yes	12

Trial	Aim	Phase	Funding	Multicentre?	International?	Country	Sufficiently powered?	Follow-up (months)
Douillard 2005[53]	To evaluate DOC + CIS vs VNB + CIS and the effect of crossover to single-agent DOC or VNB at disease progression	II	Laboratoire Sanofi-aventis, France	Yes	No	France	Yes	36
Martoni 2005[54]	To determine whether or not GEM + CIS offers any advantages over VNB + CIS	III	NR	Yes	No	Italy	Yes	24
Thomas 2006[58]	To evaluate the efficacy and safety of GEM + CARB	II	Eli Lilly and Company, France; l'assistance publique/ Hôpitaux de Marseille	Yes	No	France	Unclear	11
Chen 2007[52]	To evaluate the efficacy of DOC + CIS vs VNB + CIS	II	NR	No	No	Taiwan	Yes	12
Helbekkmo 2007[55]	To compare VNB + CARB and GEM + CARB for efficacy, HRQoL and toxicity	III	NR	Yes	No	Norway	Yes	12
Langer 2007[56]	To evaluate PAX + CARB vs GEM + CIS	II	Public Health Service Grants, National Cancer Institute, National Institutes of Health, Department of Health and Human Services	Yes	No	USA	No	24
Ohe 2007[57]	To compare efficacy and toxicity of PAX + CARB, GEM + CIS, VNB + CIS vs IRIN + CIS	III	Bristol-Myers Squibb, Japan; Eli Lilly and Company, Japan; Kyowa Hakko Kogyo Co. Ltd, Japan	Yes	No	Japan	Yes	24
Chang 2008[50]	To evaluate the safety and efficacy of GEM + CIS vs VNB + CIS	Unclear	NR	No	No	Taiwan	Unclear	12
Scagliotti 2008[61]	To compare the OS of PEM + CIS vs GEM + CIS	III	Eli Lilly and Company	Yes	Yes	Belgium, Brazil, Canada, Denmark, Germany, India, Italy, Korea, Netherlands Poland, Turkey and the USA	Yes	24

Trial	Aim	Phase	Funding	Multicentre?	International?	Country	Sufficiently powered?	Follow-up (months)
Gronberg 2009[62]	To compare PEM + CARB vs GEM + CARB	III	Eli Lilly and Company	Yes	No	Norway	Yes	12
Mok 2009[15] and Fukuoka 2011[64]	To compare efficacy, safety, and AE profile of GEF vs PAX + CARB	III	AstraZeneca	Yes	Yes	Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan and Thailand	Yes	17
Tan 2009[59]	To compare efficacy of day 1 i.v. VNB and day 8 oral VNB + CIS vs DOC + CIS	III	Institut de Recherche Pierre Fabre Pharmaceuticals Inc.	Yes	Yes	Australia, Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Mexico, Poland, Portugal, South Africa, Spain, Switzerland and Taiwan	No	12
Maemondo 2010[63]	To compare GEF vs PAX + CARB	III	Japan Society for Promotion of Science, Japanese Foundation for the Multidisciplinary Treatment of Cancer, Tokyo Cooperative Oncology Group	Yes	No	Japan	No	24
Mitsudomi 2010[65]	To compare GEF vs DOC + CIS	III	West Japan Oncology Group	Yes	No	Japan	Yes	40
Treat 2010[60]	To compare GEM + CARB or GEM + PAX vs PAX + CARB	III	Eli Lilly and Company	Yes	No	USA	Yes	36

IFOS, ifosfamide; IRIN, irinotecan; NR, not reported.

Appendix 9 Intervention details

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Kelly 2001[48]			PAX 225 mg/m^2 i.v. for 3 hours plus CARB AUC of 6 every 3 weeks 6–10 cycles		VNB 25 mg/m^2/week and CIS 100 mg/m^2 every 4 weeks 6–10 cycles	
Scagliotti 2002[43]		GEM 1250 mg/m^2 i.v. days 1 and 8 and CIS 75 mg/m^2 (with appropriate hydration and antiemetics) day 2 of a 21-day cycle 6–8 cycles	PAX 225 mg/m^2 as a 3-hour infusion then i.v. CARB AUC 6 mg/ml/minute, both on day 1 every 21 days 6–8 cycles		VNB 25 mg/m^2 days 1, 8, 15 and 22 as a 30-minute i.v. infusion and CIS 100 mg/m^2 i.v. (with appropriate hydration and antiemetics) day 1 every 28 days. After 12 weeks of treatment, VNB was administered every other week 6–8 cycles	
Schiller 2002[47]	DOC 75 mg/m^2 and CIS 75 mg/m^2 on day 1 of a 3-week cycle	GEM 1000 mg/m^2 on days 1, 8 and 15, and CIS 100 mg/m^2 on day 1 of a 4-week cycle	Arm 1: PAX 135 mg/m^2 over a 24-hour period on day 1 followed by CIS 75 mg/m^2 on day 2. The cycle was repeated every 3 weeks Arm 2: PAX 225 mg/m^2 given over a 3-hour period on day 1, followed on the same day by CARB AUC 6 mg/ml/minute in a 3-week cycle			
Fossella 2003[44]	Arm 1: DOC 75 mg/m^2 immediately followed by CIS 75 mg/m^2, both as 1-hour i.v. infusions on day 1, repeated every 3 weeks Arm 2: DOC 75 mg/m^2 as a 1-hour i.v. infusion immediately followed by i.v. CARB AUC 6 mg/ml/minute, both on day 1, repeated every 3 weeks				VNB 25 mg/m^2 as a 6–10-minute i.v. infusion on days 1, 8, 15 and 22, plus CIS 100 mg/m^2 i.v. on day 1, repeated every 4 weeks	

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gebbia 2003[49]		GEM 1400 mg/m^2 on days 1 and 8 plus CIS 100 mg/m^2 on day 8			VNB 25 mg/m^2 on days 1 and 8 plus CIS 100 mg/m^2 on day 1	
Gridelli 2003[45]		GEM 1200 mg/m^2 on days 1 and 8 plus CIS 80 mg/m^2 on day 1 plus CIS 80 mg/m^2 on day 1. All cycles were given every 3 weeks			VNB 30 mg/m^2 on days 1 and 8 plus CIS 80 mg/m^2 on day 1. All cycles were given every 3 weeks	
Smit 2003[46]		GEM 1250 mg/m^2 on days 1 and 8 and CIS 80 mg/m^2 on day 1 after GEM	PAX 175 mg/m^2 on day 1 followed by CIS 80 mg/m^2 on day 1			
Chen 2004[51]			PAX 66 mg/m^2 i.v. days 1, 8 and 15 every 4 weeks plus i.v. CIS 60 mg/m^2 on day 15		VNB 23 mg/m^2 days 1, 8 and 15 every 4 weeks plus CIS 60 mg/m^2 day 15	
Douillard 2005[53]	DOC 75 mg/m^2 as a 1-hour infusion followed by CIS 100 mg/m^2 as a 1-hour infusion on day 1, every 3 weeks for up to six cycles				CIS 100 mg/m^2 as a 1-hour infusion on day 1 followed by VNB 30 mg/m^2 as a 15-minute infusion on days 1 and 8, every 3 weeks for up to six cycles	
Martoni 2005[54]		GEM 1200 mg/m^2 on days 1 and 8 as an i.v. 30-minute infusion plus CIS 75 mg/m^2 on day 1, every 3 weeks for up to six cycles			VNB 25 mg/m^2 on days 1 and 8 as an i.v. bolus plus CIS 75 mg/m^2 on day 1, every 3 weeks for up to six cycles	
Thomas 2006[58]		CARB AUC 6 mg/ml/minute after creatinine clearance, administered as a 30-minute infusion on day 1 of a 21-day cycle (day 1–day 22 and day 43). GEM was administered at 1250 mg/m^2 as a 30-minute infusion on days 1 (after CARB) and 8			CIS 80 mg/m^2 in a 1-hour infusion on days 1, 22 and 43 with pre- and posthydration, and VNB at 30 mg/m^2 as a 20-minute infusion weekly from day 1 to day 57, every 3 weeks	

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Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Chen 2007[52]	CIS 60 mg/m^2 i.v. infusion on day 1, plus DOC 60 mg/m^2 on day 1				CIS 60 mg/m^2 i.v. infusion on day 1, plus VNB 25 mg/m^2 on days 1 and 8, every 3 weeks	
Helbekkmo 2007[55]		GEM 1000 mg/m^2 days 1 and 8, CARB AUC 4, 3-week cycles			VNB 25 mg/m^2 days 1 and 8, CARB AUC 4, day 1, 3-week cycles	
Langer 2007[56]		GEM 1000 mg/m^2 i.v. over 30 minutes on days 1 and 8 and CIS 60 mg/m^2 i.v. on day 1 over 1 hour. Cycles were repeated every 3 weeks. Routine pre-hydration and aggressive antiemetics preceded CIS	PAX 200 mg/m^2 i.v. on day 1 over 3 hours. CARB AUC 6, over 30 minutes immediately after PAX. Before PAX, all patients received routine premedication including dexamethasone, diphenhydramine (or equivalent), and cimetidine (or other H_2 blockers). Treatment was cycled at 3-week intervals, including standard antiemetic prophylaxis			
Ohe 2007[57]		CIS 80 mg/m^2 on day 1 and 1000 mg/m^2 of GEM on days 1 and 8, cycle repeated every 3 weeks	PAX 200 mg/m^2 over a 3-hour period followed by CARB AUC 6 mg/ml/minute on day 1 and cycle repeated every 3 weeks		CIS 80 mg/m^2 on day 1 and 25 mg/m^2 of VNB on days 1 and 8, cycle repeated every 3 weeks	

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Chang 2008[50]		GEM 1000 mg/m^2 on days 1, 8 and 15 (in 100 ml 5% dextrose and given over 30 minutes) in combination with CIS 80 mg/m^2 on day 15 (diluted with 500 ml normal saline) i.v. over 3 hours. Repeated every 28 days for up to six cycles			VNB 20 mg/m^2 in 100 ml dextrose over 10 minutes on days 1, 8 and 15, in combination with CIS 80 mg/m^2 on day 15 (diluted with 500 ml normal saline) i.v. over 3 hours. Repeated every 28 days for up to six cycles	
Scagliotti 2008[61]		CIS 75 mg/m^2 on day 1 plus GEM 1250 mg/m^2 on days 1 and 8, every 3 weeks for a maximum of six cycles		CIS 75 mg/m^2 plus PEM 500 mg/m^2 on day 1, every 3 weeks for a maximum of six cycles		
Gronberg 2009[62]		GEM 1000 mg/m^2 on days 1 and 8 plus CARB AUC 5 on day 1		PEM 500 mg/m^2 plus CARB area AUC 5 on day 1		
Mok 2009[15] and Fukuoka 2011[64]			PAX (200 mg/m^2 i.v. over a 3-hour period on the first day of the cycle) followed immediately by CARB AUC 5.0 or 6.0 mg/ml/minute, i.v. over a period of 15–60 minutes in cycles of once every 3 weeks for up to six cycles			GEF 250 mg/day administered orally
Tan 2009[59]	DOC 75 mg/m^2 in combination with CIS 75 mg/m^2 on day 1 every 3 weeks				VNB 25 mg/m^2 i.v. on day 1, oral VNB 60 mg/m^2 on day 8, increased in the absence of grade 3/4 haematological toxicity to VNB 30 mg/m^2 i.v. on day 1 and oral VNB 80 mg/m^2 on day 8, 3-week cycle	

DOI: 10.3310/hta17310

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Maemondo 2010[63]			PAX 200 mg/m^2, i.v. over a 3-hour period and CARB AUC 6, i.v. over a 1-hour period, both administered on the first day of every 3-week cycle for at least three cycles			GEF 250 mg/day administered orally
Mitsudomi 2010[65]	DOC 60 mg/m^2, i.v. over a 1-hour period followed by CIS 80 mg/m^2, administered i.v. over a 90-minute period, 21-day cycle					GEF 250 mg/day administered orally, 21-day cycle
Treat 2010[60]		GEM 1000 mg/m^2 infused over 30 minutes on days 1 and 8 plus CARB AUC 5.5 over 15–30 minutes on day 1	PAX 225 mg/m^2 infused over 3 hours on day 1 plus CARB AUC 6.0 over 15–30 minutes on day 1			

Appendix 10 Patient characteristics

Trial	Intervention	No. randomised	Median age (years)	% male	Disease stage		Histology			
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)	PS (%)	
Kelly 2001[48]	VNB + CIS	202	61	67	11	89	NR	NR	NR	NR
	PAX + CARB	206	62	70	12	88	NR	NR	NR	NR
Scagliotti 2002[43]	GEM + CIS	205	63	81	19	81	33	67	ECOG	0–1 = 95
	PAX + CARB	201	62	76	18	82	32	48	ECOG	0–1 = 92
	VNB + CIS	203	63	78	19	81	27	73	ECOG	0–1 = 92
Schiller 2002[47]	PAX + CIS	303	62	64	11	89	NR	NR	ECOG	0 = 29 1 = 65 2 = 6
	GEM + CIS	301	64	62	14	86	NR	NR	ECOG	0 = 33 1 = 62 2 = 5
	DOC + CIS	304	63	63	14	86	NR	NR	ECOG	0 = 32 1 = 62 2 = 6
	PAX + CARB	299	63	62	14	86	NR	NR	ECOG	0 = 28 1 = 67 2 = 5
Fossella 2003[44]	DOC + CIS	408	61	72	33	67	32	44	KPS	70 = 3.7 80–90 = 80.4 100 = 15.9
	DOC + CARB	406	59	72	33	67	33	42	KPS	70 = 3.9 80–90 = 79.8 100 = 16.3
	VNB + CIS	404	61	75	33	67	35	41	KPS	70 = 4 80–90 = 79.2 100 = 16.8

Trial	Intervention	No. randomised	Median age (years)	% male	Disease stage		Histology			
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)	PS (%)	
Gebbia 2003[49]	VNB + CIS	140	63	76	46	54	52	34	ECOG	0–1 = 83 2 = 17
	GEM + CIS	138	60	78	46	54	52	31	ECOG	0–1 = 80 2 = 20
[a]Gridelli 2003[45]	GEM + CIS/VNB + CIS	126	62	81	20	80	34	42	ECOG	0 = 32 1 = 55 2 = 14
	VNB + CIS	126								
Smit 2003[46]	PAX + CIS	159	57	60	18	82	19	40	WHO	0 = 22 1 = 66 2 = 12
	GEM + CIS	160	57	71	21	79	26	46	WHO	0 = 25 1 = 64 2 = 11
Chen 2004[51]	PAX + CIS	70	64.9 (mean)	80	27	66	14	66	WHO	0 = 19 1 = 37 2 = 44
	VNB + CIS	70	64.8 (mean)	66	23	67	23	56	WHO	0 = 11 1 = 41 2 = 47
Douillard 2005[53]	DOC + CIS	119	58	83	0	100	33	41	WHO	0 = 29 1 = 53 2 = 15
	VNB + CIS	120	57	81	0	100	32	47	WHO	0 = 40 1 = 54 2 = 11

Trial	Intervention	No. randomised	Median age (years)	% male	Disease stage		Histology		PS (%)	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)		
Martoni 2005[54]	VNB + CIS	146	62	76	32	66	29	52	KPS	Median (range): 80 (70–100)
	GEM + CIS	146	63	81	36	56	28	54	KPS	Median (range): 80 (70–100)
Thomas 2006[58]	GEM + CARB	51	60	82	12	86	35	57	ECOG	0–1 = 86 2 = 14
	VNB + CIS	49	56	84	4	96	51	35	ECOG	0–1 = 88 2 = 12
Chen 2007[52]	VNB + CIS	48	64.9	73	17	83	17	69	WHO	0 = 4 1 = 79 2 = 17
	DOC + CIS	46	60.2	57	20	80	26	54	WHO	0 = 0 1 = 72 2 = 28
Helbekkmo 2007[55]	VNB + CARB	222	67	59	30	70	27	50	WHO	0–1 = 72 2 = 28
	GEM + CARB	222	67	64	28	72	24	47	WHO	0/1 = 71 2 = 29
Langer 2007[56]	PAX + CARB	54	65	74	9	79	18	51	ECOG	2 = 54
	GEM + CIS	49	67	59	18	73	21	45	ECOG	2 = 49

Trial	Intervention	No. randomised	Median age (years)	% male	Disease stage		Histology		PS (%)	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)		
Ohe 2007[57]	PAX + CARB	150	63	68	19	81	21	72	ECOG	0 = 30 1 = 70
	GEM + CIS	151	61	69	21	79	20	74	ECOG	0 = 31 1 = 69
	VNB + CIS	150	61	70	18	82	20	75	ECOG	0 = 31 1 = 69
Chang 2008[50]	GEM + CIS	39	62.4	71	26	74	24	65	ECOG	0 = 0 1 = 53 2 = 47
	VNB + CIS	44	61.6	64	36	64	33	62	ECOG	0 = 2 1 = 62 2 = 36
Scagliotti 2008[61]	PEM + CIS	862	61.1	70	24	76	28	51	ECOG	0 = 35 1 = 64 1 unknown
	GEM + CIS	863	61	70	24	76	27	48	ECOG	0 = 36 1 = 64 2 unknown
Gronberg 2009[62]	PEM + CARB	225	64	56	29	71	26	50	WHO	0–1 = 79 2 = 21
	GEM + CARB	221	66	59	28	72	23	50	WHO	0–1 = 77 2 = 23
Mok 2009[15] and Fukuoka 2011[64]	GEF	609	57	21	25	75	NR	95	WHO	0 = 26 1 = 64 2 = 10
	PAX + CARB	608	57	21	24	76	NR	97	WHO	0 = 27 1 = 63 2 = 10

Trial	Intervention	No. randomised	Median age (years)	% male	Disease stage		Histology		PS (%)	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)		
Tan 2009[59]	VNB + CIS	194	59.4	73	19	81	34	42	KPS	80 = 38 90 = 42 100 = 19
	DOC + CIS	196	62.1	76	15	85	34	39	KPS	80 = 38 90 = 38 100 = 24
Maemondo 2010[63]	GEF	115	63.9 (mean)	37	13	77	3	90	ECOG	0 = 47 1 = 52 2 = 1
	PAX + CARB	115	62.6 (mean)	36	18	74	2	96	ECOG	0 = 50 1 = 48 2 = 2
Mitsudomi 2010[65]	GEF	88	64	31	12	48	1	97	WHO	0 = 65 1 = 35
	DOC + CIS	89	64	30	10	48	0	98	WHO	0 = 60 1 = 40
Treat 2010[60]	GEM + CARB	379	64.1	58	10	90	18	NR	ECOG	0 = 33 1 = 66 2 = 1
	PAX + CARB	379	64.1	61	11	89	16	NR	ECOG	0 = 39 1 = 60 2 = 1

NR, not reported.

a Data not reported by arm.

Appendix 11 Inclusion/exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Kelly 2001[48]	Histologically or cytologically confirmed NSCLC (primarily squamous cell, large cell, or adenocarcinoma). Patients with stage IV or selected stage IIIB disease by the International Staging System (lung cancer). Stage IIIB patients had to have a positive pleural effusion or multiple ipsilateral lung nodules. Bidimensionally measurable or assessable disease, PS of 0 or 1, neutrophil count ≥ 1500/μl, platelet count greater than or equal to institutional lower limits of normal, haemoglobin ≥ 9 mg/dl, serum creatinine ≤ 1.5 mg/dl or a calculated creatinine clearance ≥ 60 ml/minute, bilirubin level ≤ 2.0 mg/dl, AST less than or equal to twice the institutional upper limits of normal, or less than or equal to four times the institutional upper limits of normal if the patient had liver metastases. Previous surgery and radiotherapy were allowed	Prior chemotherapy or biologic therapy, brain metastases, grade 2 or higher peripheral neuropathy
Scagliotti 2002[43]	Locally advanced (stage IIIB with either pleural effusion or N3 supraclavicular nodal disease), recurrent, and/or metastatic (stage IV) NSCLC. The neoplastic disease must have been clinically assessable, as defined by objective imaging studies consistent with and supported by a pathological (histological or cytological) diagnosis of NSCLC. The presence of at least one unidimensional measurable disease was mandatory and bidimensionally measurable disease was preferable. Although patients were required to be chemotherapy or immunotherapy naive, radiotherapy was permitted if concluded at least 4 weeks before entering the study (provided the irradiated site was not the only site of measurable disease), and prior surgery was allowed if the patient met all the other criteria specified. Patients were to have an ECOG PS of 0–2 and a life expectancy of at least 12 weeks. Adequate bone marrow reserve (WBC count 3.5×10^9/l, platelets 100×10^9/l, haemoglobin 10 g/l, and haematocrit 30%) and liver and renal function (creatinine 1.5 times the upper limit of normal)	Active infection, symptomatic CNS metastases requiring emergency radiotherapy and/or corticosteroids, serious concomitant systemic disorders, second primary malignancy (except in situ carcinoma of the cervix or non-melanomatous skin cancers), and severe cardiovascular diseases. Patients who were pregnant or breast feeding
Schiller 2002[47]	Confirmed disease, measurable or non-measurable; aged at least 18 years; adequate haematological function (as indicated by a white cell count of at least 4000/mm^3 and a platelet count of at least 100,000/mm^3), hepatic function [as indicated by a bilirubin level that did not exceed 1.5 mg per decilitre (25.6μmol/l)] and renal function [as indicated by a creatinine level that did not exceed 1.5 mg per deciliter (132.6μmol/l)]. Prior radiotherapy at symptomatic sites was permitted provided that the indicator sites (the sites that were followed to determine whether or not there was a response) had not been irradiated and that the radiotherapy had been completed before chemotherapy was initiated. Patients with stable brain metastases were eligible	Prior chemotherapy

Trial	Inclusion criteria	Exclusion criteria
Fossella 2003[44]	Adults (aged ≥ 18 years) with histologically or cytologically confirmed locally advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC, KPS ≥ 70%, and at least one measurable or assessable lesion were recruited. Adequate organ function was required, as evidenced by absolute neutrophil count ≥ 1.5×10^9/l, platelet count ≥ 100×10^9/l, haemoglobin ≥ 9.0 g/dl, hepatic enzyme levels ≤ 2 × ULN range, alkaline phosphatase levels ≤ 5 × ULN, total bilirubin levels no more than the ULN, and serum creatinine levels ≤ 1.5 mg/dl (or creatinine clearance ≥ 60 ml/minute)	Prior chemotherapy treatment with a biologic response modifier, previous or concurrent malignant disease (except cone-biopsied carcinoma in situ of the cervix or adequately treated basal or squamous cell carcinoma of the skin), history of brain or leptomeningeal metastases (except if adequately treated and radiologically stable for at least 4 weeks), peripheral neuropathy of National Cancer Institute common toxicity criteria grade 2 or above, major surgery within 2 weeks of study entry, radiotherapy within 4 weeks of study entry, or other serious concomitant illness
Gebbia 2003[49]	Histologically confirmed diagnosis of locally advanced, inoperable stage IIIB (cytologically positive pleural effusion and/or supraclavicular nodes) or metastatic stage IV NSCLC; aged 18–75 years; PS < 2 according to the ECOG criteria; life expectancy of at least 3 months; adequate bone marrow function (WBC/4000/MMC, PTL/120,000/MMC, Hb/10 g%); serum bilirubin < 2 mg%, serum transaminases less than two times the normal value; serum creatinine < 1.5 mg%, BUN < 50 mg%; normal cardiac function as evaluated by ECG; no signs of CNS metastases. Absence of severe, uncontrolled metabolic, respiratory, cardiovascular, neurological and infectious diseases was mandatory. Absence of second malignancies with the exception of adequately managed in situ uterine or cutaneous basal cell carcinomas, and geographical accessibility to the oncological centres in order to guarantee a correct follow-up were also necessary prerequisites for inclusion into the trial. Previous radiotherapy was allowed if patients had measurable disease outside of radiotherapy fields. Because evaluation of ORR was one of the study aims all enrolled patients had to present bidimensionally measurable disease according to the WHO criteria	Prior chemotherapy
Gridelli 2003[45]	Histological or cytological proof of NSCLC and aged < 70 years. Stage IV disease or stage IIIB disease with malignant pleural effusion or supraclavicular nodes. ECOG PS of 0, 1 or 2; adequate haematology (absolute neutrophil count 2000/l, platelets 100,000/l, and haemoglobin 10 g/dl) and biochemistry (serum creatinine 1.25 × ULN, AST and ALT and bilirubin 1.25 × ULN, unless as a result of liver metastases); willing and able to complete QoL questionnaires. Could have received prior radiotherapy	Prior chemotherapy, brain metastases or a history of prior invasive malignancy
Smit 2003[46]	Histologically or cytologically confirmed NSCLC stage IIIB (caused by malignant pleural effusion or supraclavicular lymph nodes only) and stage IV disease according to the revised staging system of the American Joint Committee on Cancer. Aged between 18 and 76 years, WHO PS 2, measurable disease, no previous chemotherapy with the exception of prior neoadjuvant or adjuvant chemotherapy that ended > 1 year before entry, and adequate haematological, renal and hepatic function. Previous radiotherapy was allowed provided that an interval of at least 4 weeks had elapsed and the radiotherapy field did not include all measurable lesions used as target lesion. Patients with pre-existing brain metastases or leptomeningeal disease who were treated with radiotherapy, stable without medications (e.g. corticosteroids), and asymptomatic were eligible	

Trial	Inclusion criteria	Exclusion criteria
Chen 2004[51]	Cytological or histological diagnosis of NSCLC; stage IIIB, IV or recurrence after surgical treatment; aged 18–80 years; no prior chemotherapy, immunotherapy or radiotherapy; a PS of 0–2 on the WHO scale; bidimensionally measurable disease; and adequate bone marrow reserve with a WBC count ≥ 4000 mm^3, platelets ≥ 100,000 mm^3, and haemoglobin × 10 g/dl	Signs or symptoms of brain metastases; inadequate liver function (bilirubin 41.5 × ULN and ALT/AST 43 × ULN); or inadequate renal function with creatinine 42.0 mg/dl were excluded from the study
Douillard 2005[53]	Histologically or cytologically confirmed stage IV NSCLC (squamous cell, large cell, adenocarcinoma or undifferentiated NSCLC). At least one measurable or assessable lesion outside irradiated fields, i.e. cutaneous or lymph node ≥ 1010 mm assessed by clinical measurement; limited pulmonary nodule ≥ 1010 mm detected by standard chest X-ray or ≥ 2010 mm using CT scan; others lesions ≥ 2010 mm at CT scan. Age 18–75 years; WHO PS ≤ 2; and adequate bone marrow (neutrophil count ≥ 1.5 × 10^9/l, platelet count ≥ 100 × 10^9/l), renal and hepatic functions (creatinine ≤ 140 mmol/l, total bilirubin ≤ 1.5 × ULN, transaminases ≤ 2.5 × ULN, alkaline phosphatases ≤ 5 × ULN except for isolated bone metastases). Previous radiotherapy was allowed if it involved < 25% of bone marrow and was completed 4 weeks before study entry. Previously irradiated or clinically asymptomatic brain metastases and any weight loss during the last 6 months were admitted	Stages IIIB (including wet T4); National Cancer Institute Common Terminology Criteria (NCI CTC) peripheral neuropathy grade > 1; prior chemotherapy or biological therapy for metastases; lymphangitis carcinomatosa, ascites or pleural effusion as the only target
Martoni 2005[54]	Histological or cytological diagnosis of NSCLC; stages IIIB or IV, or recurrent disease after an operation for primary NSCLC; KPS) ≥ 70; no prior chemotherapy or radiotherapy; adequate marrow (granulocyte count > 1500/ll; platelet count of at least 100,000/ll), cardiac, hepatic and renal (serum creatinine < 1.5 mg/dl) functions	Symptomatic brain metastases, previous or concomitant malignancies, with the exception of in situ carcinoma of the cervix and adequately controlled, non-melanoma skin cancer
Thomas 2006[58]	Aged between 18 and 70 years, with a histological or cytological diagnosis of NSCLC, with an ECOG score ≤ 2 and a life expectancy ≥ 12 weeks. Patients had to present a stage IV disease, but without brain metastasis or stage IIIB disease with malignant pleural effusion proven by cytology. Previous radiotherapy was allowed. Normal hepatic and renal functions, and an adequate bone marrow reserve were required: total bilirubin ≤ 1.25 × ULN, AST and ALT < 3 × ULN, ALP < 2.5 × ULN, and creatinine concentration ≤ 110 mol/l, white blood cells ≥ 4 × 10^9/l with neutrophils > 1.5 × 10^9/l platelets ≥ 100 × 10^9/l, haemoglobin ≥ 10 g/dl. In addition, patients were required to have at least one bidimensionally measurable target lesion outside the irradiation field, ≥ 2 cm on a CT scan. Bone metastases and pleural or peritoneal effusions were not considered as measurable lesions	Prior chemotherapy
Chen 2007[52]	Cytological or histological diagnosis of NSCLC; stages IIIB or IV; aged 18–80 years; with no prior chemotherapy, immunotherapy, or radiotherapy; with a PS of 0–2 on the WHO scale; bidimensionally measurable disease; and adequate bone marrow reserve with a WBC count ≥ 4000 mm^3, platelets ≥ 100,000 mm^3 and haemoglobin ≥ 10 g/dl	Symptomatic brain metastases; inadequate liver function (total bilirubin > 1.5 × ULN and ALT/AST > 3 × ULN); or inadequate renal function with creatinine > 2.0 mg/dl

Trial	Inclusion criteria	Exclusion criteria
Helbekkmo 2007[55]	Chemo-naive patients with histologically or cytologically confirmed NSCLC stage IIIB or IV, not candidates for curative treatment. WHO PS 0–2 and ability to understand oral and written study information. No upper age limit was defined. WBC count > 3.0×10^9 cells 1^{-1}, platelet count > 100×10^9 cells 1^{-1}, serum creatinine < $1.5 \times$ ULN and bilirubin and serum transaminase levels < $2 \times$ ULN	Other active malignancies, pregnancy, or breast feeding
Langer 2007[56]	Advanced, incurable, chemotherapy-naive NSCLC; ECOG PS 2; age at least 18 years; adequate physiological indices, including absolute neutrophil count of at least 2000; platelets at least 100,000; creatinine ≤ 1.5 mg/dl; bilirubin ≤ 1.5 mg/dl	Prior radiotherapy to assessable disease (unless disease progression was confirmed at that site by physical examination, radiography, or pathology) or had pre-existing grade 2 or higher sensory neuropathy, CNS metastases untreated or actively growing despite prior radiation or surgery, or other active concurrent malignancies. Pregnancy, allergies to polyoxyethylate castor oil and significant comorbidities precluding chemotherapy, including active congestive heart failure and recent myocardial infarction
Ohe 2007[57]	Histologically and/or cytologically documented NSCLC, clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion > 2 cm, aged 20–74 years, ECOG PS of 0 or 1, adequate haematological, hepatic and renal functions, partial pressure of arterial oxygen (PaO_2) ‡60 torr, expected survival > 3 months, able to undergo first course treatment in an inpatient setting	Prior chemotherapy, prior surgery and/or radiotherapy for the primary site
Chang 2008[50]	Histologically confirmed stage IIIB or IV NSCLC, measurable disease, aged > 18 years, ECOG PS 2 or better, allowed to have received prior radiotherapy if performed more than 4 weeks prior to enrolment, on < 30% of the marrow-bearing bones, patients with asymptomatic brain metastasis were allowed provided it was not the only disease site, adequate baseline bone marrow, hepatic and renal function	History of prior or concomitant malignancy, pregnant or lactating women
Scagliotti 2008[61]	Chemotherapy-naive patients with histologically or cytologically confirmed NSCLC, classified as stage IIIB not amenable to curative treatment or stage IV, with at least one unidimensionally measurable lesion according to the Response Evaluation Criteria in Solid Tumors, with an ECOG PS of 0 or 1, and at least 18 years of age. Patients had adequate bone marrow reserve and organ function including calculated creatinine clearance ≥45 ml/minute based on the standard Cockcroft–Gault formula. Prior radiotherapy was permitted if it was completed at least 4 weeks before study treatment and patients had fully recovered from its acute effects	Peripheral neuropathy National Cancer Institute Common Toxicity Criteria grade 1, progressive brain metastases, or uncontrolled third-space fluid retention before study entry. Unable to interrupt aspirin and other non-steroidal anti-inflammatory drugs or if they were unable or unwilling to take folic acid, vitamin B_{12} or corticosteroids

Trial	Inclusion criteria	Exclusion criteria
Gronberg 2009[62]	Chemotherapy-naive and aged > 18 years old, stage IIIB (ineligible for curative radiotherapy) or stage IV NSCLC, WHO PS of 0 to 2, adequate bone marrow and liver function and creatinine clearance 45 ml/minute (Cockroft–Gault formula)	
Mok 2009[15] and Fukuoka 2011[64]	Aged ≥18 years, histologically or cytologically confirmed stage IIIB or IV NSCLC with histological features of adenocarcinoma (including bronchoalveolar carcinoma), non-smokers (patients who had smoked < 100 cigarettes in their lifetime) or former light smokers (stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking)	Prior chemotherapy or biological or immunological therapy
Tan 2009[59]	Between 18 and 75 years, histologically or cytologically (fine-needle aspiration) proven NSCLC, stage IIIB (with supraclavicular nodal metastases or pleural effusion), stage IV or relapsing (locally or distant) after a local treatment; KPS of ≥80%; life expectancy > 12 weeks; previously untreated with chemotherapy or immunotherapy; adequate bone marrow, hepatic and renal function; neutrophils $\geq 2.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; haemoglobin > 11 g/dl or 6.8 mmol//l; total bilirubin ≤1 × ULN; transaminases < 2.5 × ULN; alkaline phosphatases < 5 × ULN; creatinine ≤ULN or creatinine clearance ≥60 ml/minute; with the presence of at least one measurable indicator lesion (RECIST criteria) not previously irradiated and assessed by conventional CT scan (longest diameter ≥20 mm, spiral on CT scan or ≥10 mm on magnetic resonance imaging)	
Maemondo 2010[63]	Presence of advanced NSCLC harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), aged ≤75 years	History of chemotherapy
Mitsudomi 2010[65]	Initially, only patients with postoperative recurrence were eligible, because these surgical specimens were expected to ensure good sample quality. However, because of the initial slow accrual, the protocol was amended on 10 July 2006 to include patients with stage IIIB/IV disease. Histologically or cytologically confirmed NSCLC, harbouring activating EGFR mutations (either exon 19 deletion or L858R in exon 21), aged ≤75 years, WHO PS 0–1, measurable or non-measurable disease according RECIST, adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than CIS + DOC, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for PLAT doublet therapy and >1 month for oral tegafur plus uracil therapy	Previous drug therapy that had targeted EGFR, history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80. Pregnancy or lactation, or patients whose participation in the trial was judged to be inappropriate by the attending doctor

Trial	Inclusion criteria	Exclusion criteria
Treat 2010[60]	Histologically confirmed diagnosis of stage IIIB (with pleural or pericardial effusion), stage IV or recurrent NSCLC. Mixed tumours were categorised by the predominant cell type unless small-cell anaplastic elements were present, in which case the patient was ineligible. All patients were required to be ≥18 years of age and have measurable or evaluable disease (according to ECOG solid tumour criteria); an ECOG PS of 0 or 1; and adequate bone marrow reserve (neutrophils $>1500/mm^3$, platelets $>100{,}000/mm^3$), adequate hepatic function (aspartate transaminase ≤5 × institutional ULN and serum bilirubin ≤1.5 mg/dl × institutional ULN), and adequate renal function (creatinine clearance ≥40 ml/minute or serum creatinine ≤1.5 mg/dl). Stage IV patients with brain metastases were eligible provided the brain metastases were, in the opinion of the site investigator, clinically stable after treatment with surgery or radiotherapy	Prior chemotherapy for this diagnosis. No previous irradiation to the only area of measurable or evaluable disease, unless that site had subsequent progression of disease documented by physical examination, radiograph or pathology. Pregnant or breastfeeding women. Patients with a known or suspected hypersensitivity to agents that utilise polyoxyethylated castor oil

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; Hb, haemoglobin; ULN, upper limit of normal value; WBC, white blood cell;

Appendix 12 Summary results for the sensitivity analyses for mixed-treatment comparison for overall survival comparing chemotherapy with chemotherapy in population 1

TABLE 86 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for OS comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 16$), HR (95% CI)	Mixed-treatment comparison B ($n = 18$), HR (95% CI)	Mixed-treatment comparison C ($n = 18$), HR (95% CI)	Mixed-treatment comparison D ($n = 17$), HR (95% CI)	Mixed-treatment comparison E ($n = 17$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57,58]	1.09 (1 to 1.19)	1.09 (1 to 1.19)	1.07 (0.98 to 1.17)	1.09 (0.99 to 1.19)	1.09 (0.99 to 1.19)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	1.05 (0.96 to 1.15)	1.06 (0.96 to 1.16)	1.05 (0.96 to 1.15)	1.05 (0.96 to 1.15)	1.05 (0.96 to 1.15)
GEM + PLAT vs DOC + PLAT[47]	0.99 (0.86 to 1.13)	0.99 (0.86 to 1.14)	1.07 (0.93 to 1.23)	0.99 (0.86 to 1.14)	0.99 (0.87 to 1.13)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	0.96 (0.86 to 1.08)	0.97 (0.86 to 1.08)	0.98 (0.87 to 1.1)	0.96 (0.86 to 1.08)	0.96 (0.86 to 1.08)
VNB + PLAT vs DOC + PLAT[44,52,53,59]	0.91 (0.79 to 1.04)	0.9 (0.79 to 1.03)	1 (0.87 to 1.14)	0.91 (0.8 to 1.03)	0.91 (0.81 to 1.03)
PAX + PLAT vs DOC + PLAT[47]	0.94 (0.8 to 1.11)	0.93 (0.8 to 1.1)	1.02 (0.87 to 1.2)	0.95 (0.81 to 1.11)	0.95 (0.82 to 1.11)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 13 Summary results for the sensitivity analyses for mixed-treatment comparison for progression-free survival comparing chemotherapy with chemotherapy in population 1

TABLE 87 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for PFS comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 7$), HR (95% CI)	Mixed-treatment comparison B ($n = 8$), HR (95% CI)	Mixed-treatment comparison C ($n = 8$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[45,54,57]	1.06 (0.75 to 1.46)	1.07 (0.8 to 1.37)	1.06 (0.79 to 1.37)
GEM + PLAT vs PAX + PLAT[47,56,57]	1.23 (0.88 to 1.73)	1.28 (0.97 to 1.66)	1.23 (0.94 to 1.62)
GEM + PLAT vs DOC + PLAT[47]	1.07 (0.71 to 1.57)	1.08 (0.79 to 1.43)	1.08 (0.79 to 1.45)
VNB + PLAT vs PAX + PLAT[51]	1.16 (0.81 to 1.72)	1.2 (0.89 to 1.63)	1.16 (0.87 to 1.61)
VNB + PLAT vs DOC + PLAT[52,53]	1.01 (0.68 to 1.51)	1.01 (0.77 to 1.34)	1.02 (0.78 to 1.36)
PAX + PLAT vs DOC + PLAT[47]	0.87 (0.56 to 1.31)	0.85 (0.61 to 1.17)	0.88 (0.62 to 1.21)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 14 Summary results for the sensitivity analyses for mixed-treatment comparison for time to progression comparing chemotherapy with chemotherapy in population 1

TABLE 88 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for TTP comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 7$), HR (95% CI)	Mixed-treatment comparison B ($n = 7$), HR (95% CI)	Mixed-treatment comparison C ($n = 7$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[45,54]	1.06 (0.75 to 1.46)	1.07 (0.8 to 1.37)	1.06 (0.79 to 1.37)
GEM + PLAT vs PAX + PLAT[47,56]	1.23 (0.88 to 1.73)	1.28 (0.97 to 1.66)	1.23 (0.94 to 1.62)
GEM + PLAT vs DOC + PLAT[47]	1.07 (0.71 to 1.57)	1.08 (0.79 to 1.43)	1.08 (0.79 to 1.45)
VNB + PLAT vs PAX + PLAT[51]	1.16 (0.81 to 1.72)	1.2 (0.89 to 1.63)	1.16 (0.87 to 1.61)
VNB + PLAT vs DOC + PLAT[53]	1.01 (0.68 to 1.51)	1.01 (0.77 to 1.34)	1.02 (0.78 to 1.36)
PAX + PLAT vs DOC + PLAT[47]	0.87 (0.56 to 1.31)	0.85 (0.61 to 1.17)	0.88 (0.62 to 1.21)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 15 Summary results for the sensitivity analyses for mixed-treatment comparison for progression-free survival/time to progression comparing chemotherapy with chemotherapy in population 1

TABLE 89 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for PFS/TTP comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 14$), HR (95% CI)	Mixed-treatment comparison B ($n = 15$), HR (95% CI)	Mixed-treatment comparison C ($n = 15$), HR (95% CI)	Mixed-treatment comparison D ($n = 15$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[45,54]	1.05 (0.93 to 1.2)	1.06 (0.93 to 1.21)	1.07 (0.93 to 1.22)	1.06 (0.93 to 1.19)
GEM + PLAT vs PAX + PLAT[47,56]	1.08 (0.97 to 1.22)	1.14 (0.99 to 1.3)	1.12 (0.97 to 1.28)	1.12 (0.98 to 1.27)
GEM + PLAT vs DOC + PLAT[47]	1.05 (0.87 to 1.24)	1.05 (0.86 to 1.25)	1.02 (0.84 to 1.23)	1.06 (0.89 to 1.25)
VNB + PLAT vs PAX + PLAT[51]	1.03 (0.88 to 1.21)	1.08 (0.9 to 1.28)	1.05 (0.88 to 1.24)	1.06 (0.9 to 1.25)
VNB + PLAT vs DOC + PLAT[52,53]	0.99 (0.83 to 1.18)	0.99 (0.81 to 1.18)	0.96 (0.79 to 1.15)	1.00 (0.85 to 1.18)
PAX + PLAT vs DOC + PLAT[47]	0.97 (0.78 to 1.17)	0.92 (0.74 to 1.14)	0.92 (0.73 to 1.13)	0.95 (0.77 to 1.16)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 16 Summary results for the direct meta-analysis and results of the mixed-treatment comparison 1-year survival for trials comparing chemotherapy with chemotherapy in population 1

TABLE 90 Summary results for the direct meta-analysis and results of the mixed-treatment comparison (HR, 95% CI) 1-year survival for trials comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Direct meta-analysis 1 (*n* = 17) HR (95% CI)	Mixed-treatment comparison 1 (*n* = 17) HR (95% CI)	Mixed-treatment comparison A (*n* = 15), HR (95% CI)	Mixed-treatment comparison B (*n* = 17), HR (95% CI)	Mixed-treatment comparison C (*n* = 17), HR (95% CI)	Mixed-treatment comparison D (*n* = 16), HR (95% CI)	Mixed-treatment comparison E (*n* = 16), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57,58]	0.90 (0.81 to1.02)	0.93 (0.83 to 1.05)	0.94 (0.83 to 1.06)	0.94 (0.84 to 1.06)	0.95 (0.85 to 1.06)	0.93 (0.83 to 1.06)	0.93 (0.83 to 1.05)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	1.00 (0.90 to 1.10)	0.96 (0.85 to 1.08)	0.96 (0.85 to 1.08)	0.94 (0.84 to 1.06)	0.96 (0.86 to 1.07)	0.96 (0.85 to 1.08)	0.96 (0.85 to 1.08)
GEM + PLAT vs DOC + PLAT[47]	0.86 (0.69 to 1.09)[a]	0.97 (0.83 to 1.15)	0.97 (0.79 to 1.17)	0.91 (0.77 to 1.07)	0.91 (0.77 to 1.07)	0.97 (0.81 to 1.16)	0.97 (0.81 to 1.15)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	0.89 (0.78 to 1.01)	1.03 (0.89 to 1.17)	1.02 (0.88 to 1.18)	1 (0.87 to 1.14)	1.02 (0.89 to 1.16)	1.03 (0.89 to 1.18)	1.03 (0.89 to 1.18)
VNB + PLAT vs DOC + PLAT[44,52,53,59]	1.09 (0.97 to 1.23)	1.04 (0.91 to 1.19)	1.04 (0.86 to 1.23)	0.96 (0.83 to 1.11)	0.96 (0.83 to 1.1)	1.05 (0.88 to 1.22)	1.04 (0.89 to 1.2)
PAX + PLAT vs DOC + PLAT[47]	1.01 (0.79 to 1.29)[a]	1.02 (0.85 to 1.21)	1.01 (0.81 to 1.24)	0.96 (0.8 to 1.16)	0.94 (0.79 to 1.13)	1.02 (0.83 to 1.23)	1.01 (0.84 to 1.22)

a Direct evidence available. Direct meta-analysis A and mixed-treatment comparison A: sensitivity analysis excluding Chen *et al*.[52] (<24 months follow-up time) and Tan *et al*.[59] (used six cycles of chemotherapy). Direct meta-analysis B and mixed-treatment comparison B: sensitivity analysis using data from PAX + CIS instead of PAX + CARB from the Schiller *et al.* trial.[47] Direct meta-analysis C and mixed-treatment comparison C: sensitivity analysis using data from DOC + CARB instead of DOC + CIS from the Fossella *et al*. trial.[44] Direct meta-analysis D and mixed-treatment comparison D: sensitivity analysis excluding Tan *et al*.[59] (used six cycles of chemotherapy). Direct meta-analysis E and mixed-treatment comparison E: sensitivity analysis excluding Chen *et al*.[52] (<24 months follow-up time). This affects VNB + PLAT vs DOC + PLAT pair-wise comparison.

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 17 Summary results for the direct meta-analysis and results of the mixed-treatment comparison 2-year survival for trials comparing chemotherapy with chemotherapy in population 1

TABLE 91 Summary results for the direct meta-analysis and results of the mixed-treatment comparison (HR, 95% CI) 2-year survival for trials comparing chemotherapy vs chemotherapy in population 1: population with squamous disease

Reference treatment vs comparator	Direct meta-analysis 1 ($n = 16$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 16$), HR (95% CI)	Mixed-treatment comparison A ($n = 15$), HR (95% CI)	Mixed-treatment comparison B ($n = 16$), HR (95% CI)	Mixed-treatment comparison C ($n = 16$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57,58]	0.89 (0.66 to 1.21)	0.84 (0.65 to 1.11)	0.84 (0.65 to 1.11)	0.84 (0.65 to 1.11)	0.85 (0.67 to 1.1)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	1.06 (0.78 to 1.46)	1.04 (0.81 to 1.37)	1.04 (0.81 to 1.38)	1.03 (0.79 to 1.36)	1.04 (0.82 to 1.34)
GEM + PLAT vs DOC + PLAT[47]	0.86 (0.55 to 1.34)	0.95 (0.63 to 1.4)	0.96 (0.62 to 1.42)	0.96 (0.62 to 1.41)	0.89 (0.61 to 1.29)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	0.82 (0.53 to 1.28)	1.24 (0.92 to 1.66)	1.24 (0.92 to 1.67)	1.23 (0.9 to 1.65)	1.23 (0.93 to 1.62)
VNB + PLAT vs DOC + PLAT[44,53,59]	0.97 (0.56 to 1.68)	1.14 (0.76 to 1.6)	1.14 (0.75 to 1.62)	1.14 (0.76 to 1.61)	1.05 (0.73 to 1.46)
PAX + PLAT vs DOC + PLAT[47]	1.0 (0.79 to 1.59)[a]	0.92 (0.58 to 1.37)	0.92 (0.58 to 1.4)	0.93 (0.59 to 1.41)	0.86 (0.56 to 1.27)

a Direct evidence available. Direct meta-analysis A and mixed-treatment comparison A: sensitivity analysis excluding Chen *et al.*[52] (<24 months follow-up time) and Tan *et al.*[59] (used six cycles of chemotherapy). Direct meta-analysis B and mixed-treatment comparison B: sensitivity analysis using data from PAX + CIS instead of PAX + CARB from the Schiller *et al.* trial.[47] Direct meta-analysis C and mixed-treatment comparison C: sensitivity analysis using data from DOC + CARB instead of DOC + CIS from the Fossella *et al.* trial.[44] Direct meta-analysis D and mixed-treatment comparison D: sensitivity analysis excluding Tan *et al.*[59] (used six cycles of chemotherapy). Direct meta-analysis E and mixed-treatment comparison E: sensitivity analysis excluding Chen *et al.*[52] (<24 months follow-up time). This affects VNB + PLAT vs DOC + PLAT pair-wise comparison.

A HR >1 favours the reference treatment and a HR <1 favours the comparator treatment.

Appendix 18 Summary results for the sensitivity analyses for mixed-treatment comparison for overall survival comparing chemotherapy with chemotherapy in population 2

TABLE 92 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for OS comparing chemotherapy vs chemotherapy in population 2: population with non-squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 18$), HR (95% CI)	Mixed-treatment comparison B ($n = 20$), HR (95% CI)	Mixed-treatment comparison C ($n = 20$), HR (95% CI)	Mixed-treatment comparison D ($n = 19$), HR (95% CI)	Mixed-treatment comparison E ($n = 19$), HR (95% CI)	Mixed-treatment comparison F ($n = 19$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57]	1.09 (1.00 to 1.20)	1.09 (1 to 1.19)	1.07 (0.98 to 1.17)	1.09 (0.99 to 1.19)	1.09 (1.00 to 1.19)	1.09 (1.00 to 1.19)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	1.05 (0.96 to 1.15)	1.06 (0.96 to 1.16)	1.05 (0.96 to 1.16)	1.05 (0.96 to 1.15)	1.05 (0.96 to 1.15)	1.05 (0.96 to 1.15)
GEM + PLAT vs DOC + PLAT[47]	0.99 (0.86 to 1.14)	0.99 (0.86 to 1.14)	1.07 (0.93 to 1.23)	0.99 (0.86 to 1.14)	0.99 (0.87 to 1.13)	0.99 (0.86 to 1.14)
GEM + PLAT vs PEM + PLAT[61,62]	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.85 (0.74 to 0.99)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	0.96 (0.86 to 1.07)	0.97 (0.86 to 1.09)	0.98 (0.88 to 1.10)	0.96 (0.86 to 1.08)	0.96 (0.86 to 1.07)	0.96 (0.86 to 1.08)
VNB + PLAT vs DOC + PLAT[44,52,53,59]	0.91 (0.79 to 1.04)	0.91 (0.79 to 1.04)	1.00 (0.87 to 1.14)	0.91 (0.8 to 1.04)	0.91 (0.81 to 1.02)	0.91 (0.79 to 1.04)
VNB + PLAT vs PEM + PLAT	0.74 (0.61 to 0.90)	0.74 (0.61 to 0.90)	0.75 (0.62 to 0.91)	0.75 (0.61 to 0.91)	0.74 (0.61 to 0.90)	0.78 (0.66 to 0.93)
PAX + PLAT vs DOC + PLAT[47]	0.94 (0.8 0 to 1.11)	0.94 (0.80 to 1.10)	1.02 (0.86 to 1.19)	0.95 (0.81 to 1.11)	0.95 (0.82 to 1.10)	0.94 (0.81 to 1.11)
PAX + PLAT vs PEM + PLAT	0.77 (0.64 to 0.94)	0.77 (0.63 to 0.93)	0.77 (0.63 to 0.93)	0.78 (0.64 to 0.94)	0.77 (0.64 to 0.94)	0.81 (0.68 to 0.96)
DOC + PLAT vs PEM + PLAT	0.82 (0.66 to 1.02)	0.82 (0.66 to 1.02)	0.76 (0.61 to 0.94)	0.82 (0.65 to 1.02)	0.81 (0.66 to 1.01)	0.86 (0.70 to 1.05)

Appendix 19 Summary results for the sensitivity analyses for mixed-treatment comparison for progression-free survival comparing chemotherapy with chemotherapy in population 2

TABLE 93 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for PFS comparing chemotherapy vs chemotherapy in population 2: population with non-squamous disease

Reference treatment vs comparator	Mixed-treatment comparison A ($n = 8$), HR (95% CI)	Mixed-treatment comparison B ($n = 9$), HR (95% CI)	Mixed-treatment comparison C ($n = 9$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[45,54]	1.06 (0.93 to 1.21)	1.06 (0.93 to 1.21)	1.07 (0.93 to 1.22)
GEM + PLAT vs PAX + PLAT[47,56]	1.12 (0.98 to 1.28)	1.14 (0.99 to 1.30)	1.12 (0.97 to 1.28)
GEM + PLAT vs DOC + PLAT[47]	1.05 (0.87 to 1.25)	1.05 (0.86 to 1.25)	1.02 (0.84 to 1.22)
GEM + PLAT vs PEM + PLAT[63]	0.90 (0.72 to 1.12)	0.90 (0.71 to 1.14)	0.90 (0.71 to 1.14)
VNB + PLAT vs PAX + PLAT[51]	1.06 (0.89 to 1.25)	1.07 (0.90 to 1.27)	1.05 (0.88 to 1.24)
VNB + PLAT vs DOC + PLAT[52,53]	0.99 (0.83 to 1.18)	0.99 (0.82 to 1.18)	0.96 (0.79 to 1.14)
VNB + PLAT vs PEM + PLAT	0.85 (0.66 to 1.10)	0.85 (0.65 to 1.12)	0.84 (0.65 to 1.10)
PAX + PLAT vs DOC + PLAT[47]	0.94 (0.76 to 1.16)	0.92 (0.74 to 1.13)	0.91 (0.73 to 1.12)
PAX + PLAT vs PEM + PLAT	0.81 (0.62 to 1.04)	0.79 (0.61 to 1.05)	0.80 (0.62 to 1.06)
DOC + PLAT vs PEM + PLAT	0.86 (0.65 to 1.15)	0.86 (0.65 to 1.18)	0.88 (0.66 to 1.20)

Appendix 20 Summary results for the sensitivity analyses for direct meta-analysis for progression-free survival/time to progression comparing chemotherapy with chemotherapy in population 2

TABLE 94 Summary results for the sensitivity analyses for direct meta-analysis (HR, 95% CI) for PFS/TTP comparing chemotherapy vs chemotherapy in population 2: population with non-squamous disease

Reference treatment vs comparator	Meta-analysis 1 ($n = 16$), HR (95% CI)	Meta-analysis A ($n = 15$), HR (95% CI)	Meta-analysis B ($n = 16$), HR (95% CI)	Meta-analysis C ($n = 16$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,58]	1.06 (0.93 to 1.20)	1.06 (0.93 to 1.20)	1.06 (0.93 to 1.20)	1.06 (0.93 to 1.20)
GEM + PLAT vs PAX + PLAT[43,46,47,56,60]	1.05 (0.96 to 1.15)	1.05 (0.96 to 1.15)	1.08 (0.97 to 1.21)	1.05 (0.96 to 1.15)
GEM + PLAT vs DOC + PLAT[47]	0.87 (0.73 to 1.04)	0.87 (0.73 to 1.04)	0.87 (0.73 to 1.04)	0.87 (0.73 to 1.04)
GEM + PLAT vs PEM + PLAT[61]	0.90 (0.79 to 1.02)	0.90 (0.79 to 1.02)	0.90 (0.79 to 1.02)	0.90 (0.79 to 1.02)
VNB + PLAT vs PAX + PLAT[43,51]	1.21 (0.85 to 1.73)	1.21 (0.85 to 1.73)	1.21 (0.85 to 1.73)	1.21 (0.85 to 1.73)
VNB + PLAT vs DOC + PLAT[44,52,53]	0.94 (0.78 to 1.13)	0.91 (0.75 to 1.11)	0.91 (0.75 to 1.11)	0.86 (0.71 to 1.05)
VNB + PLAT vs PEM + PLAT				
PAX + PLAT vs DOC + PLAT[47]	0.97 (0.75 to 1.24)	0.97 (0.75 to 1.24)	0.97 (0.75 to 1.24)	0.97 (0.75 to 1.24)
PAX + PLAT vs PEM + PLAT				
DOC + PLAT vs PEM + PLAT				

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 21 Summary results for the sensitivity analyses for mixed-treatment comparison for progression-free survival/time to progression comparing chemotherapy with chemotherapy in population 2

TABLE 95 Summary results for the sensitivity analyses for mixed-treatment comparison (HR, 95% CI) for PFS/TTP comparing chemotherapy vs chemotherapy in population 2: population with non-squamous disease

Reference treatment vs comparator	Mixed-treatment comparison 1 ($n = 16$), HR (95% CI)	Mixed-treatment comparison A ($n = 15$), HR (95% CI)	Mixed-treatment comparison B ($n = 16$), HR (95% CI)	Mixed-treatment comparison C ($n = 16$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,58]	1.05 (0.92 to 1.19)	1.05 (0.93 to 1.20)	1.06 (0.93 to 1.21)	1.07 (0.93 to 1.22)
GEM + PLAT vs PAX + PLAT[43,46,47,56,60]	1.08 (0.97 to 1.21)	1.08 (0.97 to 1.21)	1.14 (0.99 to 1.30)	1.12 (0.97 to 1.28)
GEM + PLAT vs DOC + PLAT[47]	1.05 (0.89 to 1.24)	1.05 (0.87 to 1.24)	1.05 (0.86 to 1.25)	1.02 (0.84 to 1.22)
GEM + PLAT vs PEM + PLAT[61]	0.90 (0.74 to 1.10)	0.90 (0.73 to 1.11)	0.90 (0.71 to 1.14)	0.90 (0.71 to 1.14)
VNB + PLAT vs PAX + PLAT[43,51]	1.03 (0.89 to 1.22)	1.03 (0.88 to 1.20)	1.07 (0.90 to 1.27)	1.05 (0.88 to 1.24)
VNB + PLAT vs DOC + PLAT[44,52,53]	1.01 (0.85 to 1.18)	0.99 (0.83 to 1.18)	0.99 (0.82 to 1.18)	0.96 (0.79 to 1.14)
VNB + PLAT vs PEM + PLAT	0.86 (0.68 to 1.09)	0.85 (0.67 to 1.09)	0.85 (0.65 to 1.12)	0.84 (0.65 to 1.10)
PAX + PLAT vs DOC + PLAT[47]	0.97 (0.80 to 1.17)	0.97 (0.79 to 1.17)	0.92 (0.74 to 1.13)	0.91 (0.73 to 1.12)
PAX + PLAT vs PEM + PLAT	0.83 (0.66 to 1.04)	0.83 (0.65 to 1.05)	0.79 (0.61 to 1.05)	0.80 (0.62 to 1.06)
DOC + PLAT vs PEM + PLAT	0.85 (0.66 to 1.12)	0.86 (0.66 to 1.14)	0.86 (0.65 to 1.18)	0.88 (0.66 to 1.20)

A HR > 1 favours the reference treatment and a HR < 1 favours the comparator treatment.

Appendix 22 Summary results for the direct meta-analysis and mixed-treatment comparison for 1-year survival for trials comparing chemotherapy with chemotherapy in population 2

The following sensitivity analyses were undertaken to explore the impact of six cycles of chemotherapy, different combinations of chemotherapy and PLAT, trials with <24 month follow-up and the one study with PEM + CARB which is not licensed in the UK.

Table 96 has been removed as it includes incorrect hazard ratios caused by a reversal of the hazard ratio calculations. However, this does not impact on any of the clinical or economic results reported.

Appendix 23 Summary results for the direct meta-analysis and mixed-treatment comparison for 2-year survival for trials comparing chemotherapy with chemotherapy in population 2

The following sensitivity analyses were undertaken to explore the impact of six cycles of chemotherapy, different combinations of chemotherapy and PLAT, trials with <24 month follow-up and the one study with PEM + CARB which is not licensed in the UK.

TABLE 97 Summary results for the direct meta-analysis and mixed-treatment comparison (HR, 95% CI) for 2-year survival for trials comparing chemotherapy vs chemotherapy in population 2: population with non-squamous disease

Reference treatment vs comparator	Direct meta-analysis 1 ($n = 18$), HR (95% CI)	Mixed-treatment comparison 1 ($n = 18$), HR (95% CI)	Mixed-treatment comparison A ($n = 17$), HR (95% CI)	Mixed-treatment comparison B ($n = 18$), HR (95% CI)	Mixed-treatment comparison C ($n = 18$), HR (95% CI)	Mixed-treatment comparison F ($n = 18$), HR (95% CI)
GEM + PLAT vs VNB + PLAT[43,45,49,50,54,55,57]	0.89 (0.66 to 1.21)	0.85 (0.63 to 1.16)	0.85 (0.63 to 1.16)	0.85 (0.63 to 1.16)	0.86 (0.65 to 1.15)	0.84 (0.65 to 1.11)
GEM + PLAT vs PAX + PLAT[43,46,47,56,57,60]	1.06 (0.78 to 1.46)	1.05 (0.78 to 1.44)	1.05 (0.77 to 1.44)	1.04 (0.76 to 1.42)	1.05 (0.79 to 1.42)	1.04 (0.81 to 1.36)
GEM + PLAT vs DOC + PLAT[47]	0.86 (0.55 to 1.34)	0.94 (0.58 to 1.47)	0.94 (0.57 to 1.49)	0.94 (0.58 to 1.49)	0.88 (0.56 to 1.36)	0.96 (0.63 to 1.40)
GEM + PLAT vs PEM + PLAT[61,62]	0.91 (0.33 to 2.53)	1.06 (0.59 to 1.7)	1.05 (0.58 to 1.70)	1.05 (0.58 to 1.71)	1.08 (0.61 to 1.68)	1.47 (0.87 to 2.51)
VNB + PLAT vs PAX + PLAT[43,48,51,57]	0.82 (0.53 to 1.28)	1.23 (0.88 to 1.72)	1.24 (0.88 to 1.73)	1.22 (0.87 to 1.71)	1.22 (0.88 to 1.69)	1.24 (0.92 to 1.66)
VNB + PLAT vs DOC + PLAT[44,53,59]	0.97 (0.56 to 1.68)	1.10 (0.70 to 1.65)	1.11 (0.69 to 1.68)	1.11 (0.70 to 1.68)	1.03 (0.67 to 1.52)	1.14 (0.76 to 1.6)
VNB + PLAT vs PEM + PLAT	XX	1.24 (0.63 to 2.17)	1.24 (0.62 to 2.17)	1.24 (0.63 to 2.17)	1.26 (0.65 to 2.11)	1.76 (0.95 to 3.12)
PAX + PLAT vs DOC + PLAT[47]	1.0 (0.79 to 1.59)	0.89 (0.53 to 1.43)	0.89 (0.53 to 1.46)	0.91 (0.54 to 1.48)	0.84 (0.52 to 1.33)	0.92 (0.58 to 1.38)
PAX + PLAT vs PEM + PLAT	XX	1.01 (0.51 to 1.76)	1.01 (0.5 to 1.76)	1.02 (0.51 to 1.79)	1.03 (0.53 to 1.73)	1.42 (0.78 to 2.53)
DOC + PLAT vs PEM + PLAT	XX	1.13 (0.54 to 2.18)	1.12 (0.53 to 2.2)	1.12 (0.53 to 2.2)	1.22 (0.59 to 2.26)	1.54 (0.81 to 3.08)

XX, no direct meta-analysis or mixed-treatment comparison undertaken.

a Direct evidence available. Direct meta-analysis A and mixed-treatment comparison A: sensitivity analysis excluding Chen *et al.*[52] (<24 months follow-up time) and Tan *et al.*[59] (used six cycles of chemotherapy). Direct meta-analysis B and mixed-treatment comparison B: sensitivity analysis using data from PAX + CIS instead of PAX + CARB from the Schiller *et al.* trial.[47] Direct meta-analysis C and mixed-treatment comparison C: sensitivity analysis using data from DOC + CARB instead of DOC + CIS from the Fossella *et al.* trial.[44] Direct meta-analysis D and mixed-treatment comparison D: sensitivity analysis excluding Tan *et al.*[59] (used six cycles of chemotherapy). Direct meta-analysis E and mixed-treatment comparison E: sensitivity analysis excluding Chen *et al.*[52] (<24 months follow-up time). Direct meta-analysis F and mixed-treatment comparison F: sensitivity analysis excluding Gronberg *et al.*[62] (contains PEM + CARB which is not licensed in the UK).

A HR >1 favours the reference treatment and a HR <1 favours the comparator treatment.

Appendix 24 Adverse events, haematological grades 3–4

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Kelly 2001[48]				**PAX + CARB**		**VNB + CIS**	
	Leucopenia			G3 = 26%, G4 = 5%		G3 = 35%, G4 = 15%	
	Neutropenia			G3 = 21%, G4 = 36%		G3 = 27%, G4 = 49%	
	Thrombocytopenia			G3 = 10%, G4 = 1%		G3 = 4%, G4 = 0%	
	Anaemia			G3 = 11%, G4 = 2%		G3 = 17%, G4 = 0%	
Scagliotti 2002[43]			**GEM + CIS**	**PAX + CARB**		**VNB + CIS**	
	Neutropenia		G3 = 30.0%, G4 = 8.1%	G3 = 24.4%, G4 = 25.9%		G3 = 22.7%, G4 = 41.9%	
	Thrombocytopenia		G3 = 19.3%, G4 = 17.3%	G3 = 4.1%, G4 = 3.6%		G3 = 0%, G4 = 0.5%	
	Anaemia		G3 = 15.7%, G4 = 2.0%	G3 = 0.1%, G4 = 0%		G3 = 17.2%, G4 = 2.0%	
Schiller 2002[47]		**DOC + CIS**	**GEM + CIS**	**PAX + CIS**			
	Absolute neutrophil count	G3 = 21%, G4 = 48%	G3 = 24%, G4 = 39%	G3 = 18%, G4 = 57%			
	Platelet count	G3 = 2%, G4 = 1%	G3 = 22%, G4 = 28%	G3 = 4%, G4 = 2%			
	Anaemia	G3 = 13%, G4 = 2%	G3 = 27%, G4 = 1%	G3 = 12%, G4 = 1%			
	Infection	G3 = 5%, G4 = 2%	G3 = 4%, G4 = 2%	G3 = 4%, G4 = 4%			
	Febrile neutropenia	G3 = 1%, G4 = 10%	G3 = 1%, G4 = 3%	G3 = 2%, G4 = 14%			
				PAX + CARB			
	Absolute neutrophil count			G3 = 20%, G4 = 43%			
	Platelet count			G3 = 8%, G4 = 2%			
	Anaemia			G3 = 9%, G4 = 1%			
	Infection			G3 = 3%, G4 = 2%			
	Febrile neutropenia			G3 = 0%, G4 = 4%			

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Fossella 2003[44]		**DOC + CIS**				**VNB + CIS**	
	Leucopenia	G3–4 = 42.8%				G3–4 = 54.5%	
	Neutropenia	G3–4 = 74.8%				G3–4 = 79%	
	Thrombocytopenia	G3–4 = 2.7%				G3–4 = 3.8%	
	Anaemia	G3–4 = 6.9%				G3–4 = 24%	
	Infection	G3–4 = 8.4%				G3–4 = 7.8%	
		DOC + CARB					
	Leucopenia	G3–4 = 49.5%					
	Neutropenia	G3–4 = 74.4%					
	Thrombocytopenia	G3–4 = 7%					
	Anaemia	G3–4 = 10.5%					
	Infection	G3–4 = 11%					
Gebbia 2003[49]			**GEM + CIS**			**VNB + CIS**	
	Neutropenia		G3 = 16%, G4 = 5%			G3 = 19%, G4 = 7%	
	Haemoglobin		G3 = 18%, G4 = 1%			G3 = 13%, G4 = 1%	
	Platelets		G3 = 27%, G4 = 14%			G3 = 15%, G4 = 2%	
Gridelli 2003[45]			Either **GEM + CIS** or **VNB + CIS**			Either **GEM + CIS** or **VNB + CIS**	
	Anaemia		G3 = 6%, G4 = 1%			G3 = 6%, G4 = 1%	
	Leucopenia		G3 = 15%, G4 = 8%			G3 = 15%, G4 = 8%	
	Neutropenia		G3 = 15%, G4 = 17%			G3 = 15%, G4 = 17%	
	Infection		G3 = 3%, G4 = < 1%			G3 = 3%, G4 = < 1%	
	Thrombocytopenia		G3 = 2%, G4 = 2%			G3 = 2%, G4 = 2%	

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Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Smit 2003[46]			**GEM + CIS**	**PAX + CIS**			
	Leucocytopenia		G3–4 = 27%	G3–4 = 12%			
	Neutropenia		G3–4 = 43%	G3–4 = 34%			
	Platelets		G3–4 = 36%	G3–4 = 1%			
	Anaemia		G3–4 = 12%	G3–4 = 3%			
	Febrile neutropenia		G3–4 = 3%	G3–4 = 1%			
Chen 2004[51]				**PAX + CIS**		**VNB + CIS**	
	Leucopenia			G3 = 4.3%, G4 = 0%		G3 = 25.7%, G4 = 2.9%	
	Neutropenia			G3 = 5.7%, G4 = 4.3%		G3 = 34.2%, G4 = 18.6%	
	Anaemia			G3 = 10%, G4 = 0%		G3 = 12.9%, G4 = 1.4%	
	Thrombocytopenia			G3 = 1.4%, G4 = 0%		G3 = 0%, G4 = 0%	
Douillard 2005[53]		**DOC + CIS**				**VNB + CIS**	
	Anaemia	G3–4 = 14.8%				G3–4 = 35.1%	
	Neutropenia	G3–4 = 64.3%				G3–4 = 83.7%	
	Febrile neutropenia	G3–4 = 9.6%				G3–4 = 26.3%	
	Thrombocytopenia	G3–4 = 3.4%				G3–4 = 5.2%	
Martoni 2005[54]			**GEM + CIS**			**VNB + CIS**	
	Neutropenia		G3–4 = 17.7%			G3–4 = 30.7%	
	Anaemia		G3–4 = 3.9%			G3–4 = 7.1%	
	Thrombocytopenia		G3–4 = 9.3%			G3–4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Thomas 2006[58]			**GEM + CARB**			**VNB + CIS**	
	Neutrophils		G3 = 22%, G4 = 8%			G3 = 31%, G4 = 47%	
	Platelets		G3 = 14%, G4 = 7%			G3 = 1%, G4 = 0%	
	Haemoglobin		G3 = 8%, G4 = 5%			G3 = 8%, G4 = 2%	
	Febrile neutropenia		G3 = 1%, G4 = 1%			G3 = 4%, G4 = 3%	
Chen 2007[52]		**DOC + CIS**				**VNB + CIS**	
	Leucopenia	G3 = 34.8%, G4 = 4.3%				G3 = 31.3%, G4 = 6.3%	
	Neutropenia	G3 = 15.2%, G4 = 56.5%				G3 = 33.3%, G4 = 39.6%	
	Anaemia	G3 = 8.7%, G4 = 0%				G3 = 0%, G4 = 0%	
	Thrombocytopenia	G3 = 0%, G4 = 0%				G3 = 2.1%, G4 = 0%	
Helbekkmo 2007[55]			**GEM + CARB**			**VNB + CARB**	
	Anaemia		G3 = 16%, G4 = 3%			G3 = 6%, G4 = 0%	
	Leucopenia		G3 = 27%, G4 = 3%			G3 = 38%, G4 = 7%	
	Thrombocytopenia		G3 = 25%, G4 = 19%			G3 = 2%, G4 = 0.5%	
Langer 2007[56]			**GEM + CIS**	**PAX + CARB**			
	Neutropenia		G3 = 23%, G4 = 10%	G3 = 25%, G4 = 34%			
	Thrombocytopenia		G3 = 33%, G4 = 5%	G3 = 12%, G4 = 0%			
	Anaemia grade 3–4		G3 = 13%, G4 = 0%	G3 = 10%, G4 = 0%			
	G3–4 creatinine ≥1		G3–4 = 43%	G3–4 = 6%			

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Ohe 2007[57]			**GEM + CIS**	**PAX + CARB**		**VNB + CIS**	
	Leucocytes		G3 = 31%, G4 = 2%	G3 = 2%, G4 = 3%		G3 = 51%, G4 = 16%	
	Neutrophils		G3 = 40%, G4 = 23%	G3 = 19%, G4 = 69%		G3 = 16%, G4 = 71%	
	Haemoglobin		G3 = 22%, G4 = 5%	G3 = 13%, G4 = 12%		G3 = 25%, G4 = 5%	
	Platelets		G3 = 35%, G4 = 0%	G3 = 11%, G4=0%		G3 = 1%, G4 = 0%	
	Febrile neutropenia		G3 = 2%, G4 = 0%	G3 = 18%, G4 = 0%		G3 = 18%, G4 = 0%	
Chang 2008[50]			**GEM + CIS**			**VNB + CIS**	
	Neutropenia		G3–4 = 20%			G3–4 = 14.7%	
	Thrombocytopenia		G3–4 = 5%			G3–4 = 8.8%	
	Anaemia		G3–4 = 20%			G3–4 = 25.7%	
Scagliotti 2008[61]			**GEM + CIS**		**PEM + CIS**		
	Neutropenia		G3–4 = 26.7%		G3–4 = 15.1%		
	Anaemia haemoglobin		G3–4 = 9.9%		G3–4 = 5.6%		
	Thrombocytopenia platelets		G3–4 = 12.7%		G3–4 = 4.1%		
	Leucopenia		G3–4 = 7.6%		G3–4 = 4.8%		

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gronberg 2009[62]			**GEM + CARB**		**PEM + CARB**		
	Anaemia		G3 = 12%, G4 = 1%		G3 = 12%, G4 = 1%		
	Leucopenia		G3 = 36%, G4 = 10%		G3 = 18%, G4 = 5%		
	Granulocytopenia		G3 = 26%, G4 = 25%		G3 = 25%, G4 = 15%		
	Thrombocytopenia		G3 = 32%, G4 = 24%		G3 = 13%, G4 = 11%		
	Blood transfusions		G3–4 = 43%		G3–4 = 29%		
	Platelet transfusion		G3–4 = 9%		G3–4 = 3		
Mok 2009[15] and Fukuoka 2011[64]				**PAX + CARB**			
	Any neutropenia			G3–5 = 67.1%			G3–5 = 3.7%
	Febrile			G3–5 = 2.9%			G3–5 = 0.2%
	Anaemia			G3–5 = 10.6%			G3–5 = 2.2%
	Leucopenia			G3–5 = 35%			G3–5 = 1.5%
Tan 2009[59]		**DOC + CIS**				**VNB + CIS**	
	Neutropenia	G3 = 20.1%, G4 = 36.5%				G3 = 14.9%, G4 = 37.8%	
	Febrile neutropenia	G3/4 = 0%				G3/4 = 0%	
	Leucopenia	G3 = 29.6%, G4 = 5.3%				G3 = 19.1%, G4 = 12.2%	
	Haemoglobin	G3 = 4%, G4 = 0%				G3 = 12.8%, G4 = 1.1%	
	Thrombocytopenia	G3 = 0.5%, G4 = 0%				G3 = 2.7%, G4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Maemondo 2010[63]				**PAX + CARB**			
	Neutropenia			G3 = 33%, G4 = 33%			G3 = 0%, G4 = < 1%
	Anaemia			G3 = 5%, G4 = 0%			G3 = 0%, G4 = 0%
	Thrombocytopenia			G3 = 3%,G4 = < 1%			G3 = 0%, G4 = 0%
Mitsudomi 2010[65]		**DOC + CIS**					
	Leucocytopenia	G3–4 = 49%					G3–4 = 0%
	Thrombocytopenia	G3–4 = 0%					G3–4 = 0%
	Neutropenia	G3–4 = 84%					G3–4 = 0%
	Anaemia	G3–4 = 17%					G3–4 = 0%
Treat 2010[60]			**GEM + CARB**	**PAX + CARB**			
	Neutropenia		G3 = 25%, G4 = 14%	G3 = 13%, G4 = 21%			
	Febrile neutropenia		G3 = 2%, G4 = < 1%	G3 = 2%, G4 = < 1%			
	Thrombocytopenia		G3 = 49%, G4 = 15%	G3 = 11%, G4 = 2%			
	Platelet transfusion		G3 = 8%, G4 = 0%	G3 = < 1%, G4 = 0%			
	Anaemia		G3 = 22%, G4 = < 1%	G3 = 6%, G4 = 0%			
	Red blood cell transfusion		G3 = < 1%, G4 = 0%	G3 = 0%, G4 = 0%			
	Transfusion		G3 = 9%, G4 = 0%	G3 = 2%, G4 = 0%			

Appendix 25 Adverse events, non-haematological grades 3–4

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Kelly 2001[48]				**PAX + CARB**		**VNB + CIS**	
	Nausea			G3 = 7%, G4 = 0%		G3 = 18%, G4 = 0%	
	Sensory neuropathy			G3 = 13%, G4 = 0%		G3 = 3%, G4 = 0%	
	Vomiting			G3 = 4%, G4 = 0%		G3 = 12%, G4 = 0%	
	Fatigue			G3 = 8%, G4 = 0%		G3 = 11%, G4 = 0%	
	Hyponatraemia			G3 = 3%, G4 = 0%		G3 = 7%, G4 = 0%	
	Respiratory infection with neutropenia			G3 = 1%, G4 = 0%		G3 = 5%, G4 = 0%	
	Weakness (motor neuropathy)			G3 = 8%, G4 = 0%		G3 = 7%, G4 = 0%	
Scagliotti 2002[43]			**GEM + CIS**	**PAX + CARB**		**VNB + CIS**	
	Nausea/vomiting		G3 = 5.6%, G4 = 1.0%	G3 = 0.5%, G4 = 0%		G3 = 11.1%, G4 = 1.5%	
	Peripheral neuropathy		G3/4 = 0%	G3 = 0%		G3 = 0.5%	
	Constipation		G3 = 0.5%, G4 = 0%	G3/4 = 0%		G3 = 2.5%, G4 = 0.5%	
	Renal		G3 = 0%, G4 = 0.5%	G3/4 = 0%		G3 = 1.5%, G4 = 3.5%	
	Cardiovascular		G3 = 0.5%, G4 = 2.5%	G3 = 1.0%, G4 = 1.5%		G3 = 0.5%, G4 = 2.5%	
	Cutaneous		G3 = 0.5%, G4 = 0%	G3/4 = 0%		G3/4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Schiller 2002[47]		**DOC + CIS**	**GEM + CIS**	**PAX + CIS**			
	Cardiac toxic effects	G3 = 1%, G4 = 2%	G3 = 1%, G4 = 3%	G3 = 2%, G4 = 0%			
	Renal toxic effects	G3 = 3%, G4 = 0%	G3 = 6%, G4 = 2%	G3 = 3%, G4 = 0%			
	Nausea	G3 = 24%	G3 = 37%	G3 = 25%			
	Vomiting	G3 = 3%, G4 = 18%	G3 = 7%, G4 = 28%	G3 = 3%, G4 = 21%			
	Diarrhoea	G3 = 2%, G4 = 8%	G3 = 2%, G4 = 1%	G3 = 1%, G4 = 6%			
	Hypersensitivity reactions	G3 = 5%, G4 = 2%	G3 = 4%, G4 = 0%	G3 = 2%, G4 = 1%			
	Weakness	G3 = 15%, G4 = 1%	G3 = 17%, G4 = 0%	G3 = 13%, G4 = 1%			
	Neuropathy	G3 = 5%	G3 = 9%	G3 = 5%			
				PAX + CARB			
	Cardiac toxic effects			G3 = 1%, G4 = 1%			
	Renal toxic effects			G3 = 1%, G4 = 0%			
	Nausea			G3 = 9%			
	Vomiting			G3 = 2%, G4 = 6%			
	Diarrhoea			G3 = 1%, G4 = 1%			
	Hypersensitivity reactions			G3 = 1%, G4 = 1%			
	Weakness			G3 = 14%, G4 = 1%			
	Neuropathy			G3 = 10%			

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Fossella 2003[44]		**DOC + CIS**				**VNB + CIS**	
	Asthenia	G3–4 = 12.3%				G3–4 = 14.4%	
	Nausea	G3–4 = 9.9%				G3–4 = 16.4%	
	Pulmonary	G3–4 = 9.6%				G3–4 = 11.4%	
	Pain	G3–4 = 7.9%				G3–4 = 8.3%	
	Vomiting	G3–4 = 7.9%				G3–4 = 16.2%	
	Diarrhoea	G3–4 = 6.7%				G3–4 = 2.8%	
	Anorexia	G3–4 = 5.4%				G3–4 = 4.8%	
		DOC + CARB					
	Asthenia	G3–4 = 10.7%					
	Nausea	G3–4 = 6.2%					
	Pulmonary	G3–4 = 13.5%					
	Pain	G3–4 = 9%					
	Vomiting	G3–4 = 4.2%					
	Diarrhoea	G3–4 = 5.2%					
	Anorexia	G3–4 = 3.0%					
Gebbia 2003[49]			**GEM + CIS**			**VNB + CIS**	
	Vomiting		G3 = 22%, G4 = 1%			G3 = 20%, G4 = 1%	
	Constipation		G3 = 1%			G3 = 1%	
	Alopecia		G3 = 12%			G3 = 9%	
	Peripheral neurotoxicity		G3 = 1%			G3 = 2%	
	Transaminases		G3 = 2%			G3 = 1%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gridelli 2003[45]			Either **GEM + CIS** or **VNB + CIS**			Either **GEM + CIS** or **VNB + CIS**	
	Bleeding		G3 = 0%, G4 = < 1%			G3 = 0%, G4 = < 1%	
	Vomiting		G3 = 12%, G4 = 1%			G3 = 12%, G4 = 1%	
	Diarrhoea		G3 = < 1%, G4 = < 1%			G3 = < 1%, G4 = < 1%	
	Renal		G3 = < 1%, G4 = < 1%			G3 = < 1%, G4 = < 1%	
	Pulmonary		G3 = 1%, G4 = 1%			G3 = 1%, G4 = 1%	
	Hepatic		G3 = 2%, G4 = < 1%			G3 = 2%, G4 = < 1%	
	Fever		G3 = 1%, G4 = 0%			G3 = 1%, G4 = 0%	
	Allergy		G3 = < 1%, G4 = 0%			G3 = < 1%, G4 = 0%	
	Cutaneous		G3 = < 1%, G4 = 0%			G3 = < 1%, G4 = 0%	
	Mucositis		G3 = < 1%, G4 = < 1%			G3 = < 1%, G4 = < 1%	
	Hair loss		G3 = 6%, G4 = 0%			G3 = 6%, G4 = 0%	
	CNS		G3 = 0%, G4 = 1%			G3 = 0%, G4 = 1%	
	PNS		G3 = 1%, G4 = 0%			G3 = 1%, G4 = 0%	
	Constipation		G3 = 1%, G4 = < 1%			G3 = 1%, G4 = < 1%	
	Hearing		G3 = 2%, G4 = 0%			G3 = 2%, G4 = 0%	
	Cardiac		G3 = < 1%, G4 = 2%			G3 = < 1%, G4 = 2%	
	Fatigue		G3 = 8%, G4 = 1%			G3 = 8%, G4 = 1%	

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Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Smit 2003[46]			**GEM + CIS**	**PAX + CIS**			
	Nausea		G3–4 = 13%	G3–4 = 8%			
	Vomiting		G3–4 = 13%	G3–4 = 9%			
	Lethargy		G3–4 = 12%	G3–4 = 9%			
	Dyspnoea		G3–4 = 11%	G3–4 = 8%			
	Other skin toxicity		G3–4 = 6%	G3–4 = 11%			
	Cancer pain		G3–4 = 13%	G3–4 = 13%			
Chen 2004[51]				**PAX + CIS**		**VNB + CIS**	
	Nausea			G3 = 0%, G4 = 0%		G3 = 0%, G4 = 0%	
	Vomiting			G3 = 1.4%, G4 = 0%		G3 = 1.4%, G4 = 0%	
	Peripheral neuropathy			G3 = 4.3%, G4 = 0%		G3 = 0%, G4 = 0%	
	Asthenia			G3 = 18.6%, G4 = 0%		G3 = 7.1%, G4 = 1.4%	
	Alopecia			G3 = 0%, G4 = 0%		G3 = 0%, G4 = 0%	
	Myalgia			G3 = 2.9%, G4 = 0%		G3 = 0%, G4 = 0%	
Douillard 2005[53]		**DOC + CIS**				**VNB + CIS**	
	Nausea	G3–4 = 18.3%				G3–4 = 6.7%	
	Vomiting	G3–4 = 15.7%				G3–4 = 10.1%	
	Asthenia	G3–4 = 11.3%				G3–4 = 11.9%	
	Diarrhoea	G3–4 = 4.3%				G3–4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Martoni 2005[54]			**GEM + CIS**			**VNB + CIS**	
	Nausea/vomiting		G3–4 = 4.0%			G3–4 = 3.1%	
	Fever		G3–4 = 4.7%			G3–4 = 2.4%	
	Peripheral neuropathy		G3–4 = 0.8%			G3–4 = 0%	
	Constipation		G3–4 = 0%			G3–4 = 0%	
	Stomatitis		G3–4 = 0%			G3–4 = 0.8%	
	Alopecia		G3–4 = 8%			G3–4 = 4.8%	
	Local toxicity		G3–4 = 0%			G3–4 = 0%	
	Renal toxicity		G3–4 = 0.8%			G3–4 = 0%	
	Liver toxicity		G3–4 = 0%			G3–4 = 0%	
Thomas 2006[58]			**GEM + CARB**			**VNB + CIS**	
	Nausea/vomiting		G3–4 = 2%			G3–4 = 14%	
	Bleeding		G3–4 = 12%			G3–4 = 0%	
	Asthenia		G3–4 = 14%			G3–4 = 2%	
	Constipation		G3–4 = 2%			G3–4 = 4%	
	Neuropathy		G3–4 = 0%			G3–4 = 0%	
	Cardiac		G3–4 = 2%			G3–4 = 4%	
	Alopecia		G3–4 = 0%			G3–4 = 0%	
	Diarrhoea		G3–4 = 0%			G3–4 = 0%	
	Mucositis		G3–4 = 2%			G3–4 = 6%	
	Infection		G3–4 = 8%			G3–4 = 14%	
	Liver		G3–4 = 2%			G3–4 = 2%	
	Cough/dyspnoea		G3–4 = 0%			G3–4 = 2%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Chen 2007[52]		**DOC + CIS**				**VNB + CIS**	
	Nausea	G3 = 4.3%, G4 = 0%				G3 = 2.1%, G4 = 0%	
	Vomiting	G3 = 4.3%, G4 = 0%				G3 = 2.1%, G4 = 0%	
	Peripheral neuropathy	G3–4 = 0%				G3–4 = 0%	
	Asthenia	G3 = 6.5%, G4 = 0%				G3–4 = 0%	
	Alopecia	G3–4 = 0%				G3–4 = 0%	
	Constipation	G3–4 = 0%				G3 = 2.1%, G4 = 0%	
	Diarrhoea	G3 = 8.7%, G4 = 2.2%				G3–4 = 0%	
Helbekkmo 2007[55]	NR		NR			NR	
Langer 2007[56]			**GEM + CIS**	**PAX + CARB**			
	Nausea/vomiting		G3 = 23%, G4 = 0%	G3 = 6%, G4 = 0%			
	Sensory neuropathy		G3 = 0%, G4 = 0%	G3 = 10%, G4 = 0%			
	Fatigue		G3 = 22%, G4 = 0%	G3 = 12%, G4 = 2%			

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Ohe 2007[57]			**GEM + CIS**	**PAX + CARB**		**VNB + CIS**	
	Nausea		G3 = 23%, G4 = 0%	G3 = 11%, G4 = 0%		G3 = 14%, G4 = 0%	
	Vomiting		G3 = 14%, G4 = 0%	G3 = 5%, G4 = 0%		G3 = 7%, G4 = 0%	
	Anorexia		G3 = 26%, G4 = 1%	G3 = 17%, G4 = 1%		G3 = 20%, G4 = 1%	
	Fatigue		G3 = 3%, G4 = 0%	G3 = 2%, G4 = 1%		G3 = 3%, G4 = 0%	
	Diarrhoea		G3 = 2%, G4 = 0%	G3 = 3%, G4 = 0%		G3 = 4%, G4 = 0%	
	Constipation		G3 = 9%, G4 = 0%	G3 = 8%, G4 = 0%		G3 = 14%, G4 = 0%	
	Neuropathy (motor)		G3 = 0%, G4 = 0%	G3 = 1%, G4 = 1%		G3 = 0%, G4 = 0%	
	Neuropathy (sensory)		G3 = 0%, G4 = 0%	G3 = 3%, G4 = 0%		G3 = 0%, G4 = 0%	
	Arthralgia		G3 = 0%, G4 = 0%	G3 = 0%, G4 = 0%		G3 = 0%, G4 = 0%	
	Myalgia		G3 = 0%, G4 = 0%	G3 = 2%, G4 = 0%		G3 = 1%, G4 = 0%	
	Injection site reaction		G3 = 0%, G4 = no category	G3 = 0%, G4 = no category		G3 = 0%, G4 = no category	
	Pneumonitis		G3 = 0%, G4 = 0%	G3 = 1%, G4 = 0%		G3 = 1%, G4 = 0%	
	Creatinine		G3 = 0%, G4 = 0%	G3 = 0%, G4 = 0%		G3 = 1%, G4 = 0%	
	AST		G3 = 3%, G4 = 0%	G3 = 1%, G4 = 0%		G3 = 3%, G4 = 0%	
	Fever		G3 = 0%, G4 = 0%	G3 = 1%, G4 = 0%		G3 = 0%, G4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Chang 2008[50]			**GEM + CIS**			**VNB + CIS**	
	Vomiting		G3–4 = 36.6%			G3–4 = 16.3%	
	Mucositis		G3–4 = 0%			G3–4 = 2.9%	
	Diarrhoea		G3–4 = 2.4%			G3–4 = 0%	
	Constipation		G3–4 = 4.9%			G3–4 = 0%	
	Fever		G3–4 = 2.4%			G3–4 = 0%	
	Skin		G3–4 = 0%			G3–4 = 0%	
	Neuropathy		G3–4 = 0%			G3–4 = 2.9%	
	Fatigue		G3–4 = 24.9%			G3–4 = 5.6%	
	Myalgia		G3–4 = 2.4%			G3–4 = 2.9%	
	Oedema		G3–4 = 2.4%			G3–4 = 0%	
	Alopecia		G3–4 = 0%			G3–4 = 0%	
	Renal		G3–4 = 0%			G3–4 = 0%	
	Liver		G3–4 = 4.8%			G3–4 = 0%	
Scagliotti 2008[61]			**GEM + CIS**		**PEM + CIS**		
	Febrile neutropenia		G3–4 = 3.7%		G3–4 = 1.3%		
	Alopecia (any grade)		G3–4 = 21.4%		G3–4 = 11.9%		
	Nausea		G3–4 = 3.9%		G3–4 = 7.2%		
	Vomiting		G3–4 = 6.1%		G3–4 = 6.1%		
	Dehydration (any grade)		G3–4 = 2.0%		G3–4 = 3.6%		
	Fatigue		G3–4 = 4.9%		G3–4 = 6.7%		

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gronberg 2009[62]			**GEM + CARB**		**PEM + CARB**		
	Neutropenic infection		G3–4 = 9%		G3–4 = 8%		
	Infections without neutropenia		G3–4 = 9%		G3–4 = 9%		
	Nausea		G3–4 = 4%		G3–4 = 3%		
	Thrombocytopenic bleedings		G3–4 = 4%		G3–4 = 2%		
	Deep-vein thrombosis		G3–4 = 1%		G3–4 = 0%		
	Lung embolism		G3–4 = 2%		G3–4 = 0%		
	Acute myocardial infarction		G3–4 = 1%		G3–4 = 1%		
	Mucositis		G3–4 = 0%		G3–4 = 1%		
	Other		G3–4 = 6%		G3–4 = 2%		

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Mok 2009[15] and Fukuoka 2011[64]				**PAX + CARB**			**GEF**
	Rash or acne			G3–5 = 0.8%			G3–5 = 3.1%
	Diarrhoea			G3–5 = 1.4%			G3–5 = 3.8%
	Dry skin			G3–5 = 0%			G3–5 = 0%
	Anorexia			G3–5 = 2.7%			G3–5 = 1.5%
	Pruritus			G3–5 = 0.2%			G3–5 = 0.7%
	Stomatitis			G3–5 = 0.2%			G3–5 = 0.2%
	Asthenic conditions			G3–5 = 1.9%			G3–5 = 0.3%
	Nausea			G3–5 = 1.5%			G3–5 = 0.3%
	Paronychia			G3–5 = 0%			G3–5 = 0.3%
	Vomiting			G3–5 = 2.7%			G3–5 = 0.2%
	Constipation			G3–5 = 0.2%			G3–5 = 0%
	Alopecia			G3–5 = 0%			G3–5 = 0%
	Neurotoxic effects			G3–5 = 4.9%			G3–5 = 0.3%
	Myalgia			G3–5 = 1.7			G3–5 = 0.5%
	Arthralgia			G3–5 = 1.0%			G3–5 = 0.2%

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Tan 2009[59]		**DOC + CIS**				**VNB + CIS**	
	Tinnitus	G3–4 = 0%				G3–4 = 0%	
	Abdominal pain	G3 = < 1%, G4 = 0%				G3 = 2%, G4 = 0%	
	Constipation	G3 = 1%, G4 = 0%				G3 = < 1%, G4 = 0%	
	Diarrhoea	G3 = 6%, G4 = 0%				G3 = 2%, G4 = 0%	
	Dyspepsia	G3–4 = 0%				G3–4 = 0%	
	Nausea	G3 = 5%, G4 = 0%				G3 = 7%, G4 = 0%	
	Stomatitis	G3–4 = 0%				G3 = 2%, G4 = 0%	
	Vomiting	G3 = 6%, G4 = 0%				G3 = 9%, G4 = < 1%	
	Fatigue	G3 = 6%, G4 = 0%				G3 = 4%, G4 = 1%	
	Injection site reaction	G3–4 = 0%				G3 = < 1%, G4 = 0%	
	Pyrexia	G3 = 1%, G4 = 0%				G3–4 = 0%	
	Weight decreased	G3–4 = 0%				G3–4 = 0%	
	Anorexia	G3 = 3%, G4 = 0%				G3 = 3%	
	Dizziness	G3 = < 1%, G4 = 0%				G3–4 = 0%	
	Dysgeusia	G3–4 = 0%				G3–4 = 0%	
	Paraesthesia	G3–4 = 0%				G3 = < 1%, G4 = 0%	
	Peripheral sensory neuropathy	G3–4 = 0%				G3–4 = 0%	
	Alopecia	G3–4 = 0%				G3–4 = 0%	

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Maemondo 2010[63]				**PAX + CARB**			
	Diarrhoea			G3–4 = 0%			G3–4 = 1%
	Appetite loss			G3–4 = 6%			G3–4 = 5%
	Fatigue			G3–4 = 1%			G3–4 = 3%
	Rash			G3–4 = 3%			G3–4 = 5%
	Neuropathy (sensory)			G3–4 = 6%			G3–4 = 0%
	Arthralgia			G3–4 = 7%			G3–4 = 1%
	Pneumonitis (note: one patient had G5 effect)			G3–4 = 0%			G3–4 = 3%
	Aminotransferase elevation			G3–4 = 1%			G3–4 = 26%
Mitsudomi 2010[65]		**DOC + CIS**					
	Rash	G3–4 = 0%					G3–4 = 2%
	AST	G3–4 = 1%					G3–4 = 16%
	ALT	G3–4 = 2%					G3–4 = 28%
	Dry skin	G3–4 = 0%					G3–4 = 0%
	Diarrhoea	G3–4 = 0%					G3–4 = 1%
	Fatigue	G3–4 = 2%					G3–4 = 2%
	Paronychia	G3–4 = 0%					G3–4 = 1%
	Stomatitis	G3–4 = 0%					G3–4 = 0%
	Nausea	G3–4 = 3%					G3–4 = 1%
	Constipation	G3–4 = 0%					G3–4 = 0%
	Alopecia	G3–4 = 0%					G3–4 = 0%
	Sensory disturbance	G3–4 = 0%					G3–4 = 1%

Trial	AE	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Treat 2010[60]			**GEM + CARB**	**PAX + CARB**			
	Haemorrhage		G3 = 2%, G4 = < 1%	G3 = 0%, G4 = 0%			
	Infection		G3 = 2%, G4 = < 1%	G3 = 2%, G4 = < 1%			
	Nausea		G3 = 6%, G4 = 0%	G3 = 6%, G4 = < 1%			
	Vomiting		G3 = 4%, G4 = 0%	G3 = 4%, G4 = < 1%			
	Diarrhoea		G3 = 1%, G4 = < 1%	G3 = 2%, G4 = 0%			
	Sensory neuropathy		G3 = 2%, G4 = < 1%	G3 = 10%, G4 = < 1%			
	Arthralgia		G3–4 = < 1%	G3–4 = 2%			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; NR, not reported; PNS, peripheral nervous system.

Appendix 26 Toxic deaths

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Kelly 2001[48]			5/203		8/197	
Scagliotti 2002[43]		8/205	3/201		7/201	
Schiller 2002[47]	18/297	12/293	15/300			
Fossella 2003[44]	NR				NR	
Gebbia 2003[49]		0			0	
Gridelli 2003[45]		NR			NR	
Smit 2003[46]		2/160	4/159			
Chen 2004[51]			0		1/70	
Douillard 2005[53]	3/115				10/118	
Martoni 2005[54]		0			1/137	
Thomas 2006[58]		1/51			3/49	
Chen 2007[52]	NR				NR	
Helbekkmo 2007[55]		4/214			2/218	
Langer 2007[56]		0	1/54			
Ohe 2007[57]		1/49	1/150		0	
Chang 2008[50]		1/39			0	
Scagliotti 2008[61]		6/830		9/839		
Gronberg 2009[62]		NR		NR		
Mok 2009[15] and Fukuoka 2011[64]			15/589			23/607
Tan 2009[59]	3/196				1/194	
Maemondo 2010[63]			0			1/114
Mitsudomi 2010[65]	0					1/87
Treat 2010[60]		15/356	15/366[a]			

NR, not reported.

a Includes all deaths without evidence of progressive disease.

Appendix 27 Treatment administration

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Kelly 2001[48]			PAX + CARB 15% discontinued therapy because of toxicity. Overall, 27% completed therapy as planned. The every-3-weeks schedule of PAX + CARB was more convenient than weekly VNB with CIS. In the PAX + CARB arm, patients received 97% and 94% of the planned PAX and CARB doses, respectively		VNB + CIS More patients (28%) discontinued therapy because of toxicity ($p = 0.001$). Overall, 15% of patients on the VNB arm completed therapy as planned ($p = 0.008$). Over six cycles, patients treated with VNB and CIS received 78% of the intended CIS dose and 65% of the intended VNB dose	
Scagliotti 2002[43]		Total number cycles delivered for GEM + CIS arm was 825 (mean per patient 4.0 cycles). Dose reductions and omissions were 12% and 6%. Actual dose intensities were 90.6% for GEM and 100% for CIS (with GEM)	Total number cycles delivered for PAX + CARB arm was 851 (mean per patient 4.2 cycles). Dose reductions and omissions were 13% and 0%. Actual dose intensities were 94.7% for PAX and 99.2% for CARB		Total number cycles delivered = 653 (mean per patient 3.2 cycles). Dose reductions (17%) and omissions (19%), mainly because of haematological toxicities. Actual dose intensities were 77.4% for VNB and 94.8% for CIS (with VNB)	
Schiller 2002[47]	NR	NR	NR			
Fossella 2003[44]	DOC + CIS Median number treatment cycles delivered = 5.0 (over 15 weeks) combined RDI = 0.94; completed at least six cycles = 49.8%; treatment delays = 11.8% DOC + CARB Median number treatment cycles delivered = six (18 weeks) combined RDI = 0.93; completed at least six cycles = 51.4%; treatment delays = 11.2%				Median number treatment cycles delivered = 4.0 (16 weeks) combined RDI = 0.78; completed at least six cycles = 33.6%; treatment delays = 16.1%	

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gebbia 2003[49]		Total of 610 cycles with a mean of 4.3 cycles per patient. Programmed dose intensity of 25 mg/m^2/week for CIS, 700 mg/m^2/week for GEM (estimated for four cycles). Actual delivered dose intensities = 22.5 mg/m^2/week for CIS (90%) and 590 mg/m^2/week for GEM (84%), mainly due to myelosuppression, asthenia and mild renal toxicity			Total of 659 cycles, mean of 4.7 cycles per patient. Programmed dose intensity of 25 mg/m^2/week for CIS and 12.5 mg/m^2/week for VNB. Actual delivered dose intensity of CIS and VNB calculated in patients who received four cycles of chemotherapy = 22.7 mg/m^2/week (91%) and 11.5 mg/m^2/week (92%), respectively. Overall, dose reduction was performed in 19% of cycles owing to toxicity, which was mainly represented by myelosuppression, neurological and mild renal side effects	
Gridelli 2003[45]		NR			NR	
Smit 2003[46]		Median number of cycles = 5.0, RDI was not different between the treatment arms	Median number of cycles = 5.0, RDI was not different between the treatment arms			
Chen 2004[51]			281 cycles; mean 4.01 cycles; mean percentage dose administered was 95.3% scheduled PAX dose on day 1, 90% on day 8, and 85.2% on day 15, and 88.9% scheduled CIS dose on day 15		307 cycles; mean 4.39 cycles; mean percentage dose administered was 93.1% scheduled VNB dose on day 1, 95.3% on day 8, and 83.3% on day 15, and 87.6% of the scheduled CIS dose on day 15	

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Douillard 2005[53]	Total of 544 combination cycles were given as first line with a median of 6.0 (range: 1–6) cycles; median dose intensity = > 98% of planned dose for both drugs; majority of combination therapy cycles were administered on time (93%); 38 cycles (7%) were delayed because of haematological (14 cycles), non-haematological toxicities (14 cycles) and for other reasons unrelated to treatment (10 cycles). During combination therapy, the dose of DOC was reduced in 13 cycles (2.4%) and in 17 (3.1%) cycles for CIS				Total of 519 combination cycles were given as first line with a median of 6.0 (range: 1–6) cycles; median dose intensity was 88% (VNB) to 90% (CIS) of planned dose; majority of combination therapy cycles were administered on time (73.4%); 138 (26.6%) cycles were delayed for haematological (92 cycles, 66.7%) and non-haematological toxicities (27 cycles, 19.6%), and one cycle for both types of toxicity and 18 (13%) for other reasons. VNB was reduced in 34 cycles (6.6%) and CIS was reduced in 53 (10.2%) cycles	
Martoni 2005[54]		Median number cycles per patient = 6.0 (range: 1–7); mean percentages of doses actually administered as compared with the planned dose in the scheduled time intervals during the administration of the CIS combinations were 88.9% for GEM and 98.9% for CIS (with GEM)			Median number cycles per patient = 6.0 (range: 1–10); mean percentages of doses actually administered as compared with the planned dose in the scheduled time intervals during the administration of the CIS combinations were 86.8% for VNB and 96.6% for CIS (with VNB)	

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Thomas 2006[58]		Total of 190 cycles were administered with a median of 4.0 cycles per patient. Dose intensity was 84.9% for GEM and 99.8% for CARB. Treatment was delayed for 13.7% of cycles; median number of days per cycle was 21. The ratio between theoretical duration of chemotherapy and real duration calculated is 95.1%			Total of 172 cycles were administered, median of 3.0 cycles per patient. Dose intensity was 97.7% for CIS and 67.7% for VNB. Treatment delayed 19.2% of cycles; median number of days per cycle was 21. The ratio between theoretical duration of chemotherapy and real duration calculated is 93.8%	
Chen 2007[52]	209 cycles (median 5)				230 cycles (median five)	
Helbekkmo 2007[55]		Mean number of cycles = 2.6. 167 (78%) received all three cycles, 17 (8%) two cycles, 26 (12%) one cycle and 4 (2%) no chemotherapy. Delayed or cancelled GEM at day 8 due to haematological toxicity = 18.1% (delayed 10.2%; not given 7.9%) ($p = 0.03$). Time exceeding 24 days between the main chemotherapy courses = 23% ($p = 0.06$)			Mean number of cycles = 2.7. 180 patients (83%) received all three cycles, 21 (10%) two cycles, 15 (7%) one cycle and 2 (1%) no chemotherapy. Delayed or cancelled VNB at day 8 due to haematological toxicity = 9.3% (delayed 4.6%; not given 4.8%) ($p = 0.03$). Time exceeding 24 days between the main chemotherapy courses = 15% ($p = 0.06$)	
Langer 2007[56]		Median number of cycles administered = three per arm, 31% of 47 treated patients completed all six cycles, 10% received more than six cycles, and 46% received at least four	Median number of cycles administered = three per arm, 27% of 51 patients completed all six cycles, 11% received more than six cycles, and 49% received at least four			
Ohe 2007[57]		NR	NR		NR	

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Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Chang 2008[50]	Of the 73 eligible patients, 160 courses were administered to 34 patients. The mean number of courses = 4.7; number of courses administered per patient did not differ significantly between the two arms ($p = 0.221$). 60% of patients received the full-schedule chemotherapy doses without dose modification or delay. Compliance was insignificantly ($p = 0.062$) favorable for the GEM + CIS arm				166 courses administered to 39 patients, mean number of courses = 4; 34% of patients received the full-schedule chemotherapy doses without dose modification or delay	
Scagliotti 2008[61]		Median number of cycles = 5.0, GEM + CIS dose reductions were most commonly attributable to neutropenia, thrombocytopenia, febrile neutropenia and leucopenia. On day 8, 339 GEM doses (9.3%) were omitted. Delivered dose intensities were higher for PEM + CIS (95.0% and 94.8%, respectively) than for GEM + CIS (93.5% and 85.8%, respectively)		Median number of cycles = 5.0, dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with PEM + CIS compared with GEM + CIS, even when considering the more frequent GEM dosing (days 1 and 8 for GEM vs only day 1 for PEM). On day 1, PEM + CIS dose reductions were much less frequent (CIS, $n = 64$; PEM, $n = 54$ vs CIS, $n = 154$; GEM, $n = 362$), mainly caused by neutropenia Delivered dose intensities were higher for PEM + CIS (95.0% and 94.8%, respectively) than for GEM + CIS (93.5% and 85.8%, respectively)		

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Gronberg 2009[62]		Mean number cycles = 3.1; GEM on day 8 was omitted in 79 (12%) of 675 cycles; chemotherapy discontinued as a result of toxicity in 5% of the patients (PEM + CARB: 4%, GEM + CARB: 6%; $p = 0.51$)		Mean number of cycles = 3.3 ($p = 0.037$). Significantly more patients completed four cycles (PEM + CARB: 72%, GEM + CARB: 62%; $p = 0.030$), four cycles without delays (PEM + CARB: 58%, GEM + CARB: 44%; $p = 0.004$), and four cycles without dose reductions (PEM + CARB: 50%, GEM + CARB: 20%; $p < 0.001$)		
Mok 2009[15] and Fukuoka 2011[64]			Mean duration of treatment = 3.4 months (median 4.1 months; range 0.7–5.8 months). Median number of treatment cycles = 6.0, all patients had discontinued study treatment at data cut-off			Mean duration of treatment = 6.4 months (median 5.6 months; range 0.1–22.8 months). 24.5% of the patients continued to receive study treatment at data cut-off

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Tan 2009[59]	807 cycles were delivered, without delay in 90.5% cycles. Reasons for cycle delays for haematological/ non-haematological toxicity were reported in 8.8%/20.0% of cycles. At least one dose reduction during the trial was reported in 30 (15.7%) patients. Number of doses reduced for related haematological toxicity on day 1 of the cycle was similar in both arms. Among 172 patients receiving second cycle, 122 cycles (70.9%) were given with escalated doses. Planned six cycles of treatment were delivered in 98 of 191 patients; mean numbers of cycles = 4.4, with 129 patients having completed four cycles in both arms. RDI = 96.3% for DOC and 96.6% for CIS				807 cycles were delivered without delay in 81.3% cycles; reasons for cycle delays for haematological/ non-haematological toxicity were reported in 48.3%/6.6% of cycles. 708 cycles of oral VNB were delivered on day 8 with or without delay for 97.7%. Reason for the day 8 delay was haematological toxicity in 9 of 16 affected cycles (56.3%). At least one dose reduction during the trial was reported in 37 (19.5%) patients. Planned six cycles of treatment were delivered in 85 of 190 patients; the mean numbers of cycles = 4.2 with 124 patients having completed four cycles in both arms. RDI = 92% for i.v. VNB, 83.6% for oral VNB and 93.7% for CIS	
Maemondo 2010[63]			NR			NR
Mitsudomi 2010[65]	Median number of cycles = 4, or 64 days (range 1–6 cycles, or 1–106 days)					Median exposure = 165 days (range 22–1100 days)

Trial	DOC + PLAT	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT	GEF
Treat 2010[60]		Median number of cycles administered = 4.0, mean number of cycles administered = 3.9, percentage of patients receiving a maximum six cycles = 36.5%, median RDI = 82.9% for GEM and 94.6% for CARB, percentage of patients receiving dose adjustments = 75.8% for GEM and 62.1% for CARB. During therapy, the rates of discontinuation due to excessive complication or toxicity were 12.4%	Median number of cycles administered = 4.0, mean number of cycles administered = 3.7, percentage of patients receiving a maximum six cycles = 30.6%, median RDI = 98.2% for PAX and 95.2% for CARB, percentage of patients receiving dose adjustments = 32.2% for PAX and 33.9% for CARB. During therapy, the rates of discontinuation due to excessive complication or toxicity were 15.3%			

NR, not reported.

Appendix 28 Quality of life

Reference	Tool	QoL	Compliance
Kelly 2001[48]	FACT-L version 3	With the three categories of improved, stable and declined, there were no statistically significant treatment arm differences in QoL at 13 weeks ($p = 0.97$) or 25 weeks ($p = 0.74$)	QoL initiated halfway through the trial; thus, only 123 patients on the VNB + CIS arm and 122 patients on the PAX + CARB arm could have completed the baseline FACT-L questionnaire. Of this group, 91% of patients submitted a FACT-L questionnaire at baseline. Follow-up submission rates were 68% at 13 weeks and 47% at 25 weeks
Scagliotti 2002[43]	EORTC QLQ-C30-LC13	After two cycles of chemotherapy, only six of the functional and symptom scales of the EORTC QLQ-C30-LC13 showed treatment differences: role functioning (patients' ability to work or participate in leisure activities), fatigue, nausea/vomiting, anorexia, peripheral neuropathy and alopecia Further analysis showed that there were no statistical differences between the GEM + CIS and VNB + CIS arms. However, the PAX + CARB arm differed significantly from the VNB + CIS arm, with role functioning, fatigue, nausea/vomiting and anorexia favouring the PAX + CARB arm, and peripheral neuropathy and alopecia favouring the VNB + CIS arm When the same analysis was conducted after four cycles of therapy, the only scales showing treatment differences were pain, nausea/vomiting, peripheral neuropathy and alopecia. Further analysis showed a statistical difference between the GEM + CIS and VNB + CIS arms in peripheral neuropathy, which favoured the GEM + CIS arm. This analysis also showed statistical differences between the PAX + CARB and VNB + CIS arms for pain, peripheral neuropathy and alopecia, all of which favoured the VNB + CIS arm. Only nausea/vomiting, peripheral neuropathy and alopecia showed sustained treatment differences	Compliance at baseline was high (93–95%), but at later cycles, the percentage of patients still receiving therapy and who completed the questionnaire decreased
Schiller 2002[47]	NR	NR	NR
Fossella 2003[44]	LCSS and EQ-5D	Patients treated with either DOC + CARB or DOC + CIS reported consistently improved global QoL compared with patients treated with VNB + CIS, who generally experienced a deterioration in QoL. For patients treated with DOC + CARB, this overall advantage in global QoL was statistically significant according to both LCSS ($p = 0.016$) and EuroQol ($p < 0.001$) assessments. For patients treated with DOC + CIS, the advantage in global QoL was statistically significant when evaluated by EuroQol ($p = 0.016$), but not when evaluated by the LCSS ($p = 0.064$)	The baseline EuroQol questionnaire was completed by 831 patients (DOC + CIS, 281; DOC + CARB, 279; VNB + CIS, 271) and 811 patients (DOC + CIS, 279; DOC + CARB, 269; VNB + CIS, 263) completed the baseline LCSS questionnaire

Reference	Tool	QoL	Compliance
Gebbia 2003[49]	NR	NR	NR
Gridelli 2003[45]	EORTC QLQ-C30 and QLQ-C30	There were no significant differences in global QoL scores between the two arms (GEM + CIS and VNB + CIS were assessed as one CIS-based arm vs GEM + VNB) after 2 months of treatment. Worsening scores for appetite, vomiting and alopecia were significantly more common in the GEM + CIS and VNB + CIS arms compared with GEM + VNB Baseline mean scores were comparable between the two arms for all of the QoL items. At the planned point for primary QoL analysis (general QoL and health status at the end of cycle 2) no difference was observed between arms ($p = 0.94$); the observed effect size was just 0.06 Role and emotional functioning had higher (better) scores with GEM + VNB; at week 1 (corresponding to day 8 of cycle 1), mean changes were always worse in the GEM + CIS and VNB + CIS Loss of appetite, fatigue, vomiting and hair loss were worse in the GEM + CIS and VNB + CIS, across all of the periods, particularly at week 1 for the former three symptoms Slight advantages in cough, shoulder pain and analgesic consumption were seen among patients receiving GEM + CIS and VNB + CIS treatment Overall, in both arms, almost 40% of patients exhibited an improved global QoL and one fourth of patients remained stable. After adjustment for possible confounding variables, significant differences were seen only for appetite, vomiting and hair loss (all symptoms were worse in GEM + CIS and VNB + CIS)	Overall, 209 patients in the PLAT-based arm and 206 patients in the GEM + VNB arm were analysed. There were no differences in any of the compliance parameters between the two study arms. The rate of completed questionnaires, out of on-treatment patients, declined slightly to 84% (172 of 205), 75% (148 of 197), 85% (140 of 165) and 80% (111 of 139) in the PLAT-based arm and to 82% (163 of 199), 81% (157 of 194), 74% (129 of 174) and 74% (110 of 149) in the GEM + VNB arm at assessments made at weeks 1, 3, 6 and 9, respectively
Smit 2003[46]	NR	When comparing GEM + CIS with PAX + CIS, no significant difference in global QoL ($p = 0.816$) was observed. A statistically ($p < 0.0001$) and clinically significant overall improvement was observed for peripheral neuropathy and alopecia in GEM + CIS compared with PAX + CIS. Nausea and vomiting increased significantly with time, but at a similar rate in both arms. Clinically relevant improvement was observed for coughing and insomnia in both arms	Compliance at baseline and throughout the active treatment period was > 60%, but decreased dramatically at cycle 6 (47 forms received of the 183 forms expected; 25.7%) and for assessments during follow-up. This analysis is, therefore, restricted to the treatment period. There was no significant difference in compliance at the different assessment points between the two experimental arms and the standard arm

Reference	Tool	QoL	Compliance
Chen 2004[51]	LCSS	There was no statistically significant difference between the PAX + CIS and VNB + CIS arms, either before or two cycles after treatment, or when the patient went off study. This held true whether scored by the patients (nine items) or by the observers (six items), and included the categories of loss of appetite, fatigue, cough, dyspnoea, haemoptysis, pain, disease severity, daily activity and QoL Loss of appetite and pain were worse after two cycles of treatment in the PAX + CIS arm When considering all the treated patients together, there was a slight, although significant decrease in the scores of all items except haemoptysis	124 patients (62 patients in each arm) completed the baseline LCSS questionnaire, and after two cycles of treatment and/or after going off study
Douillard 2005[53]	NR	NR	NR
Martoni 2005[54]	NR	NR	NR
Thomas 2006[58]	NR	NR	NR
Chen 2007[52]	LCSS	No statistically significant difference in the scales between the DOC + CIS and VNB + CIS arms, either before or after two cycles of treatment, or when the patient went off study, and whether scored by the patients (nine items) or by the observers (six items) Cough and dyspnoea were worse in the VNB + CIS arm before treatment When considering all the treated patients together, there was a slight, but significant, decrease in the scores of all items, except haemoptysis, either after two cycles of treatment or after the patient had gone off study	89 patients (43 patients in the DOC + CIS arm and 46 in the VNB + CIS arm) completed LCSS questionnaire
Helbekkmo 2007[55]	EORTC QLQ-C30 and QLQ-LC13	There was no difference between the VNB + CARB and GEM + CARB arms with respect to mean change of scores or AUC from baseline to week 17	Completion of the HRQoL questionnaires was 95% and 98% at baseline and declined to minimum 61% and 60% during the 49-week follow-up for the VNB + CARB and GEM + CARB arms, respectively
Langer 2007[56]	NR	NR	NR
Ohe 2007[57]	FACT-L Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoLACD)	No statistically significant difference in global QoL was observed among the four treatment groups	NR
Chang 2008[50]	NR	NR	NR
Scagliotti 2008[61]	NR	NR	NR

Reference	Tool	QoL	Compliance
Gronberg 2009[62]	HRQoL	No clinically relevant differences in mean score between the treatment arms for either of the primary HRQoL end points. The difference in mean score between PEM + CARB and GEM + CARB and the difference in mean score from baseline through the treatment period did not exceed 10 points on any of the scales at any time point. In addition, there were no statistically significant differences in AUC for global QoL ($p = 0.72$), nausea/vomiting ($p = 0.55$), fatigue ($p = 0.55$) or dyspnoea ($p = 0.48$). Furthermore, the sensitivity test did not show any differences in AUC. There were no clinically relevant or statistically significant differences between the treatment arms on the other HRQoL scales, although there was a trend to better physical functioning and less alopecia on the PEM + CARB arm	Patients completed 2017 (87%) of 2310 HRQoL questionnaires (deceased patients excluded) during the first 20 weeks. Compliance was similar in the two groups (PEM + CARB: 98% to 80%, GEM + CARB: 99% to 78%)
Mok 2009[15] and Fukuoka 2011[64]	FACT-L and TOI	Significantly more patients in GEF than in PAX + CARB had a clinically relevant improvement in QoL (odds ratio 1.34; 95% CI 1.06 to 1.69; $p = 0.01$) and by scores on the TOI (odds ratio 1.78; 95% CI 1.40 to 2.26; $p < 0.001$). Rates of reduction in symptoms were similar between GEF and PAX + CARB (odds ratio with GEF 1.13; 95% CI 0.90 to 1.42; $p = 0.30$)	NR
Tan 2009[59]	LCSS	No significant difference between the two arms for appetite, asthenia, cough, dyspnoea, haemoptysis and pain. The average symptom burden as assessed by the LCSS was similar in the two arms. The global score was similar in DOC + CIS and VNB + CIS arms, showing a worsening from baseline to cycle 6 relative to the disease evolution	149 patients in the VNB + CIS arm (78.4%) and 152 patients in the DOC + CIS arm (79.6%) were assessable for the QoL LCSS questionnaire
Maemondo 2010[63]	NR	NR	NR
Mitsudomi 2010[65]	NR	NR	NR

NR, not reported.

Appendix 29 Details of economic search strategies

Ovid MEDLINE(R) 1950 to week 4 August 2010

	Searches	Results
1	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	23,160
2	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	21,657
3	1 or 2	26,877
4	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	199,797
5	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	280,385
6	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	25,914
7	or/4-6	392,244
8	3 and 7	12,588
9	economics/	25,894
10	exp "costs and cost analysis"/	152,116
11	exp "economics, hospital"/ or economics, medical/ or economics, pharmaceutical/	26,871
12	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	318,362
13	Cost-benefit analysis/	49,110
14	(cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.	64,892
15	exp models economic/	7359
16	*"Quality of Life"/	37,041
17	or/9-16	447,437
18	8 and 17	518
19	limit 18 to english language	474

EMBASE 1980 to 2010 week 35

	Searches	Results
1	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	27,369
2	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	34,657
3	1 or 2	38,286
4	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	161,094
5	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	337,591
6	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	33,767
7	exp Cancer Radiotherapy/ or exp Chemotherapy/	276,380
8	or/4-7	542,914
9	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	402,412
10	(value adj2 money).ti,ab.	840
11	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti,ab.	80,632
12	exp pharmacoeconomics/ or exp "health care cost"/ or health economics/ or exp "drug cost"/ or exp economic evaluation/ or exp "cost benefit analysis"/ or *"quality of life"/	397,734
13	or/9-12	656,181
14	3 and 8 and 13	1376
15	limit 14 to (human and english language and embase)	1055

Appendix 30 Details of probabilistic sensitivity analysis: hazard ratios

Correlation matrices for the estimated HRs were employed to obtain correlated random variables using the Cholesky decomposition, including both the mixed-treatment comparison estimated correlations and the PFS/OS proportions described in *Chapter 4, Hazard ratios*.

Mixed-treatment comparison estimated HRs and CIs relative to PAX were used to derive estimated standard errors for the logarithm of each HR (see *Table 57*).

Randomly sampled estimates of each HR were then computed using the formula:

$$HR_{psa} = \exp\{\ln(\text{mean HR}) - Z_{psa} \times (\text{standard error HR})\} \quad (1)$$

where Z_{psa} is sampled from the standard normal distribution.

TABLE 98 Correlation matrix of HRs relative to PAX used to generate correlated random variables for PSA: population 1

	Measure						
		PFS	PFS	PFS	OS	OS	OS
Measure	Treatment	VNB	GEM	DOC	VNB	GEM	DOC
PFS	**VNB**	1	0.6799	0.6216	0.43	0	0
PFS	**GEM**	0.6799	1	0.6174	0	0.48	0
PFS	**DOC**	0.6216	0.6174	1	0	0	0.41
OS	**VNB**	0.43	0	0	1	0.6479	0.5853
OS	**GEM**	0	0.48	0	0.6479	1	0.5313
OS	**DOC**	0	0	0.41	0.5853	0.5313	1

TABLE 99 Correlation matrix of HRs relative to PAX used to generate correlated random variables for PSA: population 2

	Measure							
		PFS	PFS	PFS	PFS	OS	OS	OS	OS
Measure	Treatment	VNB	GEM	DOC	PEM	VNB	GEM	DOC	PEM
PFS	**VNB**	1	0.6403	0.5989	0.3273	0.43	0	0	0
PFS	**GEM**	0.6403	1	0.5964	0.5176	0	0.48	0	0
PFS	**DOC**	0.5989	0.5964	1	0.3043	0	0	0.41	0
PFS	**PEM**	0.3273	0.5176	0.3043	1	0	0	0	0.57
OS	**VNB**	0.43	0	0	0	1	0.6319	0.5762	0.2855
OS	**GEM**	0	0.48	0	0	0.6319	1	0.5212	0.4618
OS	**DOC**	0	0	0.41	0	0.5762	0.5212	1	0.2369
OS	**PEM**	0	0	0	0.57	0.2855	0.4618	0.2369	1

Appendix 31 Details of probabilistic sensitivity analysis: other variables

Variable	Mean	SE	A	B	Distribution
PFS fatality	0.16	0.016	–	–	Normal
PFS fit for second-line chemotherapy	0.3449	–	1299	2467	Beta
Chemotherapy day-case administration cost (first visit)	£309.17	£14.73	–	–	Normal
Chemotherapy day-case administration cost (other visits)	£284.45	£8.95	–	–	Normal
Chemotherapy outpatient administration cost	£128.69	£3.92	–	–	Normal
Chemotherapy inpatient administration cost	£462.88	£12.88	–	–	Normal
Body surface area (males)	1.8905	0.00913	–	–	Normal
Body surface area (females)	1.6549	0.00906	–	–	Normal
Gender balance (proportion males)	56.07%	–	16,807	13,170	Beta
AE rates: DOC diarrhoea	6.41%	–	99	1445	Beta
AE rates: DOC fatigue	9.01%	–	139	1403	Beta
AE rates: DOC febrile neutropenia	2.85%	–	44	1498	Beta
AE rates: DOC hair loss	0.00%	–	0	1542	Beta
AE rates: DOC nausea/vomiting	20.36%	–	314	1228	Beta
AE rates: DOC neutropenia	62.13%	–	958	584	Beta
AE rates: DOC rash	0.00%	–	0	1542	Beta
AE rates: VNB diarrhoea	1.81%	–	23	1249	Beta
AE rates: VNB fatigue	10.75%	–	173	1436	Beta
AE rates: VNB febrile neutropenia	6.57%	–	103	1464	Beta
AE rates: VNB hair loss	1.16%	–	18	1531	Beta
AE rates: VNB nausea/vomiting	20.27%	–	354	1392	Beta
AE rates: VNB neutropenia	63.12%	–	1102	644	Beta
AE rates: VNB rash	0.14%	–	1	700	Beta
AE rates: PAX diarrhoea	2.28%	–	49	2096	Beta
AE rates: PAX fatigue	7.15%	–	153	1988	Beta
AE rates: PAX febrile neutropenia	4.95%	–	124	2383	Beta
AE rates: PAX hair loss	0.00%	–	0	2145	Beta
AE rates: PAX nausea/vomiting	13.52%	–	339	2168	Beta
AE rates: PAX neutropenia	57.36%	–	1438	1069	Beta
AE rates: PAX rash	0.45%	–	8	1771	Beta
AE rates: GEM diarrhoea	1.77%	–	31	1716	Beta
AE rates: GEM fatigue	11.69%	–	203	1533	Beta

Variable	Mean	SE	A	B	Distribution
AE rates: GEM febrile neutropenia	2.75%	–	62	2190	Beta
AE rates: GEM hair loss	1.35%	–	26	1898	Beta
AE rates: GEM nausea/vomiting	19.12%	–	505	2136	Beta
AE rates: GEM neutropenia	37.15%	–	981	1660	Beta
AE rates: GEM rash	0.46%	–	5	1088	Beta
AE rates: PEM diarrhoea	1.33%	–	11	819	Beta
AE rates: PEM fatigue	6.75%	–	56	774	Beta
AE rates: PEM febrile neutropenia	1.33%	–	11	819	Beta
AE rates: PEM hair loss	0.00%	–	0	830	Beta
AE rates: PEM nausea/vomiting	11.23%	–	117	925	Beta
AE rates: PEM neutropenia	20.63%	–	215	827	Beta
AE rates: PEM rash	0.12%	–	1	829	Beta
AE rates: GEF diarrhoea	3.09%	–	25	783	Beta
AE rates: GEF fatigue	0.87%	–	7	801	Beta
AE rates: GEF febrile neutropenia	0.12%	–	1	807	Beta
AE rates: GEF hair loss	0.00%	–	0	808	Beta
AE rates: GEF nausea/vomiting	0.62%	–	5	803	Beta
AE rates: GEF neutropenia	2.85%	–	23	785	Beta
AE rates: GEF rash	3.34%	–	27	781	Beta
AE rates: ERL diarrhoea	1.53%	–	14	904	Beta
AE rates: ERL fatigue	3.27%	–	30	888	Beta
AE rates: ERL febrile neutropenia	0.00%	–	0	918	Beta
AE rates: ERL hair loss	0.00%	–	0	918	Beta
AE rates: ERL nausea/vomiting	0.65%	–	6	912	Beta
AE rates: ERL neutropenia	0.00%	–	0	918	Beta
AE rates: ERL rash	8.00%	–	73	840	Beta
AE unit cost: nausea/vomiting/diarrhoea	£443.54	£14.80	–	–	Normal
AE unit cost: fatigue	£2536.95	£74.46	–	–	Normal
AE unit cost: febrile neutropenia	£521.67	£29.03	–	–	Normal
AE unit cost: neutropenia	£1034.99	£57.59	–	–	Normal
AE unit cost: rash	£113.03	£3.85	–	–	Normal
Response rate: DOC	26.7%	–	408	1119	Beta
Stable disease rate: DOC	39.1%	–	597	930	Beta
Response rate: PAX	27.5%	–	618	1632	Beta
Stable disease rate: PAX	34.1%	–	767	1483	Beta
Response rate: VNB	28.6%	–	418	1041	Beta
Stable disease rate: VNB	36.5%	–	533	926	Beta
Response rate: GEM	27.3%	–	560	1488	Beta

Variable	Mean	SE	A	B	Distribution
Stable disease rate: GEM	38.5%	–	789	1259	Beta
Response rate: PEM	30.6%	–	233	529	Beta
Stable disease rate: PEM	41.2%	–	314	448	Beta
Response rate: GEF	71.5%	–	236	94	Beta
Stable disease rate: GEF	19.4%	–	64	266	Beta
Response rate: DOC (second line)	6.3%	–	11	164	Beta
Stable disease rate: DOC (second line)	39.4%	–	69	106	Beta
Response rate: ERL (second line)	8.9%	–	38	389	Beta
Stable disease rate: ERL (second line)	36.1%	–	154	273	Beta
Nafees *et al.*[116] utility model parameter: intercept (stable)	0.6532	0.02223	–	–	Normal
Nafees *et al.*[116] utility model parameter: progressive disease	–0.1798	0.02169	–	–	Normal
Nafees *et al.*[116] utility model parameter: response	0.0193	0.006556	–	–	Normal
Nafees *et al.*[116] utility model parameter: diarrhoea	–0.08973	0.01543	–	–	Normal
Nafees *et al.*[116] utility model parameter: fatigue	–0.09002	0.01633	–	–	Normal
Nafees *et al.*[116] utility model parameter: febrile neutropenia	–0.07346	0.01849	–	–	Normal
Nafees *et al.*[116] utility model parameter: hair loss	–0.04802	0.01618	–	–	Normal
Nafees *et al.*[116] utility model parameter: nausea/vomiting	–0.0468	0.01553	–	–	Normal
Nafees *et al.*[116] utility model parameter: neutropenia	–0.04495	0.01482	–	–	Normal
Nafees *et al.*[116] utility model parameter: rash	–0.03248	0.01171	–	–	Normal
Place of death: hospital	55.79%	–	16,636	13,180	Beta
Place of death: hospice	16.90%	–	5039	24,777	Beta
Unit cost: chest X-ray	£24.04	£2.40	–	–	Normal
Unit cost: CT scan (two areas)	£145.83	£3.43	–	–	Normal
Unit cost: CT scan (three areas)	£162.25	£4.81	–	–	Normal
Unit cost: ECG	£32.69	£2.05	–	–	Normal
Unit cost: community nurse	£78.00	£7.80	–	–	Normal
Unit cost: GP surgery visit	£36.00	£3.60	–	–	Normal
Unit cost: clinical nurse specialist	£91.00	£9.10	–	–	Normal
Unit cost: GP home visit	£120.00	£12.00	–	–	Normal
Unit cost: therapist	£42.00	£4.20	–	–	Normal
Unit cost: long-stay inpatient episode	£2655.55	£70.71	–	–	Normal
Unit cost: long-stay inpatient excess days	£196.61	£6.25	–	–	Normal
Frequency in PFS: outpatient visits	9.612	0.332	–	–	Normal
Frequency in PFS: chest X-ray	6.785	0.279	–	–	Normal
Frequency in PFS: CT scan (chest)	0.618	0.084	–	–	Normal

APPENDIX 31

Variable	Mean	SE	A	B	Distribution
Frequency in PFS: CT scan (other)	0.355	0.064	–	–	Normal
Frequency in PFS: ECG	1.041	0.109	–	–	Normal
Frequency in PPS: outpatient visits	7.907	0.343	–	–	Normal
Frequency in PPS: chest X-ray	6.498	0.310	–	–	Normal
Frequency in PPS: CT scan (chest)	0.237	0.059	–	–	Normal
Frequency in PPS: CT scan (other)	0.415	0.079	–	–	Normal
Frequency in PPS: ECG	0.875	0.114	–	–	Normal
Time-to-death exponential rate	0.1359	0.0068	–	–	Normal

SE, standard error.

EME
HS&DR
HTA
PGfAR
PHR

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