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First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer (Review)

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TABLE OF CONTENTS

[Intervention Review]

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer

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ABSTRACT

Background

Epidermal growth factor receptor (EGFR) mutation positive (M+) non-small cell lung cancer (NSCLC) is emerging as an important subtype of lung cancer comprising 10% to 15% of non-squamous tumours. This subtype is more common in women than men and is less associated with smoking.

Objectives

To assess the clinical effectiveness of single -agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFR M+ NSCLC compared with other cytotoxic chemotherapy (CTX) agents used alone or in combination, or best supportive care (BSC). The primary outcome was overall survival. Secondary outcomes included progression-free survival, response rate, toxicity, and quality of life.

Search methods

We conducted electronic searches of the the Cochrane Register of Controlled Trials (CENTRAL) (2015, Issue 6), MEDLINE (1946 to 1 June 2015), EMBASE (1980 to 1 June 2015), and ISI Web of Science (1899 to 1 June 2015). We also searched the conference abstracts of the American Society for Clinical Oncology and the European Society for Medical Oncology (1 June 2015); Evidence Review Group submissions to the National Institute for Health and Care Excellence; and the reference lists of retrieved articles.

Selection criteria

Parallel randomised controlled trials comparing EGFR-targeted agents (alone or in combination with cytotoxic agents or BSC) with cytotoxic chemotherapy (single or doublet) or BSC in chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC unsuitable for treatment with curative intent.

Data collection and analysis

Two review authors independently identified articles, extracted data, and carried out the 'Risk of bias' assessment. We conducted meta-analyses using a fixed-effect model unless there was substantial heterogeneity, in which case we also performed a random-effects analysis as a sensitivity analysis.

Main results

Nineteen trials met the inclusion criteria. Seven of these exclusively recruited people with EGFR M+ NSCLC; the remainder recruited a mixed population and reported results for people with EGFR M+ NSCLC as subgroup analyses. The number of participants with EGFR M+ tumours totalled 2317, of whom 1700 were of Asian origin.

Overall survival (OS) data showed inconsistent results between the included trials that compared EGFR-targeted treatments against cytotoxic chemotherapy or placebo.

Erlotinib was the intervention treatment used in eight trials, gefitinib in seven trials, afatinib in two trials, and cetuximab in two trials. The findings of one trial (FASTACT 2) did report a statistically significant OS gain for participants treated with erlotinib plus cytotoxic chemotherapy when compared to cytotoxic chemotherapy alone, but this result was based on a small number of participants (n = 97). For progression-free survival (PFS), a pooled analysis of 3 trials (n = 378) demonstrated a statistically significant benefit for erlotinib compared with cytotoxic chemotherapy (hazard ratio (HR) 0.30; 95% confidence interval (CI) 0.24 to 0.38).

In a pooled analysis with 491 participants administered gefitinib, 2 trials (IPASS and NEJSG) demonstrated a statistically significant PFS benefit of gefitinib compared with cytotoxic chemotherapy (HR 0.39; 95% CI 0.32 to 0.48).

Afatinib (n = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of 2 trials (HR 0.42; 95% CI 0.34 to 0.53).

Commonly reported grade 3/4 adverse events for afatinib, erlotinib, and gefitinib monotherapy were rash and diarrhoea. Myelosuppression was consistently worse in the chemotherapy arms, fatigue and anorexia were also associated with some chemotherapies.

No statistically significant PFS or OS benefit for cetuximab plus cytotoxic chemotherapy (n = 81) compared to chemotherapy alone was reported in either of the two trials.

Six trials reported on quality of life and symptom improvement using different methodologies. For each of erlotinib, gefitinib, and afatinib, 2 trials showed improvement in one or more indices for the tyrosine-kinase inhibitor (TKI) compared to chemotherapy.

The quality of evidence was high for the comparisons of erlotinib and gefitinib with cytotoxic chemotherapy and for the comparison of afatinib with cytotoxic chemotherapy.

Authors' conclusions

Erlotinib, gefitinib, and afatinib are all active agents in EGFR M+ NSCLC patients, and demonstrate an increased tumour response rate and prolonged progression-free survival compared to cytotoxic chemotherapy. We also found a beneficial effect of the TKI compared to cytotoxic chemotherapy. However, we found no increase in overall survival for the TKI when compared with standard chemotherapy. Cytotoxic chemotherapy is less effective in EGFR M+ NSCLC than erlotinib, gefitinib, or afatinib and is associated with greater toxicity. There were no data supporting the use of monoclonal antibody therapy.

PLAIN LANGUAGE SUMMARY

First-line treatment of advanced non-small cell lung cancer identified as being EGFR mutation positive

Background

Lung cancer is the most common cancer in the world. As it shows few symptoms, it has often spread by the time it is diagnosed. Consequently surgery is usually not possible, and drug treatment, typically chemotherapy, is required.

The most common type of lung cancer is non-small cell lung cancer (NSCLC). Around 10% to 15% of people with NSCLC will have a specific kind of cancer known as epidermal growth factor receptor positive (EGFR M+) in which there are specific changes to the cancer cells in the genes controlling tumour growth. In this review we looked at new treatments that can target EGFR M+ NSCLC to find out how well they work.

Objectives

The purpose of this review was to find out whether people given treatments targeted at EGFR M+ NSCLC live longer and have a better quality of life than those having standard chemotherapy.

Trial characteristics

We found 19 trials that looked at four different EGFR-targeted drugs: erlotinib, gefitinib, afatinib, and the antibody cetuximab. We included trials reporting results up to June 2015.

Results

Our results showed that people given erlotinib, gefitinib, or afatinib have a longer time before the cancer progresses and experience fewer side effects than those people given standard chemotherapy, which is most commonly cisplatin plus one other drug. However, the people given erlotinib, gefitinib, or afatinib did not live any longer than those given standard chemotherapy. Treatment with cetuximab combined with chemotherapy did not delay further lung cancer spread and did not extend life compared with chemotherapy alone.

Conclusion

Erlotinib, gefitinib, and afatinib delay further spread of EGFR M+ lung cancer and improve quality of life, but do not extend life. Giving cetuximab with chemotherapy is no better at controlling this type of cancer or extending life than chemotherapy alone.

Summary of findings for the main comparison. Erlotinib vs control

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive (M+) non-squamous non-small cell lung cancer (NSCLC): erlotinib comparisons

Patient or population: EGFR M+ patients with NSCLC

Settings: oncology

Intervention: erlotinib

Comparison: control (cytotoxic chemotherapy)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Erlotinib				
Overall survival	56 per 100	54 per 100 (46 to 63)	HR 0.95 (0.75, 1.22)	429 (3 studies)	High	All trials were open label but included blinded independent review
Progression-free survival	73 per 100	33 per 100 (27 to 40)	HR 0.30 (0.24, 0.38)	595 (4 studies)	High	All trials were open label but included blinded independent review

*The basis for the assumed risk is calculated as the event rate in the treatment group
The corresponding risk is calculated as the assumed risk x the risk ratio (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk)))/assumed risk
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 2. Gefitinib vs paclitaxel + carboplatin

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive (M+) non-squamous non-small cell lung cancer (NSCLC): gefitinib comparisons

Patient or population: EGFR M+ patients with NSCLC

Settings: oncology

Intervention: gefitinib

Comparison: paclitaxel + carboplatin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Paclitaxel + carboplatin	Gefitinib				
Overall survival	67 per 100	66 per 100 (58 to 73)	HR 0.95 (0.77 to 1.18)	489 (2 studies)	High	Both trials were open label. IPASS did not report independent blinded review
Progression-free survival	89 per 100	57 per 100 (50 to 65)	HR 0.39 (0.32 to 0.48)	485 (2 studies)	High	Both trials were open label. IPASS did not report independent blinded review

*The basis for the assumed risk is calculated as the event rate in the treatment group
The corresponding risk is calculated as the assumed risk x the risk ratio (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk)))/assumed risk
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 3. Afatinib vs chemotherapy

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive (M+) non-squamous non-small cell lung cancer (NSCLC): afatinib comparisons

Patient or population: EGFR M+ patients with NSCLC

Settings: oncology

Intervention: afatinib

Comparison: cytotoxic chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cytotoxic chemotherapy	Afatinib				
Overall survival	46 per 100	44 per 100 (37 to 52)	HR 0.93 (0.74 to 1.17)	709 (2 studies)	High	Both trials were open label but included blinded independent central review
Progression-free survival	56 per 100	29 per 100 (24 to 35)	HR 0.42 (0.34 to 0.53)	709 (2 studies)	High	Both trials were open label but included blinded independent central review

*The basis for the assumed risk is calculated as the event rate in the treatment group
The corresponding risk is calculated as the assumed risk x the risk ratio (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk)))/assumed risk
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK (Cancer Research UK). Globally, in 2012, 1.8 million people were diagnosed with lung cancer, representing 12.9% of all cancers (GLOBOCAN 2012). In the UK in 2012, 45,000 new cases of lung cancer were diagnosed, 13% of all new cancers (Cancer Research UK 2012b). In both men and women, smoking is the primary cause of lung cancer (Cancer Research UK 2013). Prognosis is poor, as early-stage lung cancer is often asymptomatic, and the majority of patients are diagnosed at a late stage. (Cancer Research UK 2012b). In the UK in 2012, 35,000 people died of lung cancer, representing 22% of all deaths from cancer in the UK (Cancer Research UK 2012a).

Non-small cell lung cancer (NSCLC) accounts for the majority (85% to 90%) of lung cancer cases in the UK and comprises two main histological subgroups: squamous cell carcinoma and non-squamous cell carcinoma (Cancer Research UK 2012c). Squamous cell carcinoma accounts for 25% to 30% of all NSCLC cases, whilst non-squamous cell carcinoma (including adenocarcinoma and large cell carcinoma) accounts for 29% of NSCLC cases. Approximately 12% to 13% of patients have NSCLC that is 'not-otherwise specified' with the diagnosis based on cytology alone (NLCA 2015; Schiller 2002). The prognosis for people with NSCLC is poor, with a median survival of the order of six months.

Treatment for people with NSCLC depends not only on the histological subtype and genetic subtype of the tumour, but also on disease stage, comorbidity, and performance status. Chemotherapy, in most cases comprising a cisplatin doublet, for advanced disease can extend overall survival by several months compared to best supportive care and improves quality of life (Brown 2013).

In recent years the biological subtypes of NSCLC have become relevant to the selection of treatment regimens. Attention has been drawn to tumours that harbour the epidermal growth factor receptor mutation (EGFR M+). The EGFR, a protein located on the cell surface, binds to and activates epidermal growth factor. This binding induces receptor dimerisation and tyrosine kinase autophosphorylation, leading through signal transduction to cell proliferation (Han 2012; NCBI). It is estimated that 10% to 15% of people with non-squamous NSCLC have tumours that are EGFR M + (Peters 2012; Rosell 2012). An EGFR mutation is more frequently observed in never-smokers than ever-smokers (51% versus 10%), in adenocarcinomas compared to cancers of other histologies (40% versus 3%), in people of East Asian ethnicity versus other ethnicities (30% versus 8%), and in females rather than males (42% versus 14%) (Rosell 2009; Scoccianti 2012; Ulivi 2012).

The identification of people with EGFR M+ tumours has led to the development of targeted therapies comprising small molecule tyrosine kinase inhibitors (TKIs) directed at the signal transduction pathway between the cell membrane and the nucleus, while monoclonal antibodies (MABs) bind to and inactivate the receptor on the cell membrane. Since the majority of the phase III trials in this review were started, it has become apparent that activating mutations in exons 19 and 21 are associated with response to the TKIs, while the 1% of tumours with the exon 20 T790M mutation are resistant. The TKIs are orally administered agents, while the MABs are given intravenously. People of interest to this review were chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC who were not suitable for treatment with curative intent, such as surgery or radical radiotherapy.

Description of the intervention

In Europe, there are three licensed treatments that target EGFR M + NSCLC: afatinib, erlotinib, and gefitinib. These drugs are TKIs of EGFR and target proteins on the cancer cells related to activation of the signal transduction pathway. These treatments are taken orally (tablets) daily until the disease progresses. Other drugs, for example the TKI dacomitinib and the MAB cetuximab, are currently under clinical investigation and are not yet licensed for the first-line treatment of people with EGFR M+ NSCLC. We did not assess newer drugs that target the exon 20 T790M mutation in this review.

In the UK, the National Institute for Health and Care Excellence has recommended the use of monotherapy erlotinib, NICE 2012, monotherapy gefitinib, NICE 2010, and more recently, monotherapy afatinib, NICE 2014, for the first-line treatment of EGFR M+ NSCLC. In Europe, European Society for Medical Oncology guidelines recommend first-line treatment with monotherapy afatinib, erlotinib, or gefitinib (Reck 2014). In the USA, the Food and Drug Administration has approved the use of monotherapy erlotinib and monotherapy afatinib (FDA 2013; FDA 2014). Globally, there is considerable variation in the use of each of these drugs to treat people with NSCLC and in the availability and quality control of mutation testing, which determines patient selection.

Why it is important to do this review

Treatments for people with NSCLC have been evolving rapidly following the Medical Research Council meta-analysis that demonstrated improved survival for chemotherapy compared with best supportive care (MRC 1995). Until early 2000, people with NSCLC were offered standard cytotoxic chemotherapy treatments (for example cisplatin, docetaxel, vinorelbine, paclitaxel, and gemcitabine), often given in two-drug platinum-based combinations (Brown 2013). However, in recent years patients have been treated with drugs according to their histological subtype (for example pemetrexed plus cisplatin for non-squamous disease). Even more recently, as understanding of NSCLC has evolved, targeted treatments have been developed to treat specific groups of patients based on molecular criteria, for example TKIs and MABs. It is estimated that around 10% (n = 4000 annually) of all lung cancer patients in the UK have locally advanced or metastatic EGFR M+ NSCLC (NICE 2010), with a higher prevalence in Asian populations. It is therefore important to synthesise evidence for the clinical effectiveness and toxicity of these new treatments to ensure that patients are being treated with the most clinically effective drugs for their specific disease subtype.

OBJECTIVES

To assess the clinical effectiveness of single-agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFR M+ NSCLC compared with other cytotoxic chemotherapy agents used alone or in combination, or best supportive care (BSC). The primary outcome was overall survival. Secondary outcomes included progression-free survival, response rate, toxicity, and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel randomised controlled trials (RCTs).

Types of participants

Chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC unsuitable for treatment with curative intent with surgery or radical radiotherapy. We included studies that included or excluded exon 20 T790 in the review.

Types of interventions

EGFR M+ targeted agents, alone or in combination with cytotoxic agents, compared with cytotoxic agents used alone or in combination or BSC.

We excluded trials comparing single-agent or combinations of cytotoxic chemotherapy without a targeted therapy in either arm and trials with targeted therapy in both arms, and we did not evaluate maintenance or second-line strategies. We also excluded cross-over trials.

Types of outcome measures

Primary outcomes

1. Overall survival

Secondary outcomes

1. Progression-free survival
2. Tumour response
3. Toxicity and adverse effects of treatment
4. Quality of life (e.g. Functional Assessment of Cancer Therapy - Lung (FACT-L) and Trial Outcome Index (TOI))
5. Symptom palliation

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for relevant published literature up to 1 June 2015. We did not restrict searches by language.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 6) Appendix 1
- MEDLINE (from 1980) (accessed via PubMed and OvidSP) Appendix 2
- EMBASE (from 1946) (OvidSP) Appendix 3
- ISI Web of Science (from 1899) Appendix 4

We ran an initial search in October 2012. We ran an updated search (updated by the Cochrane Lung Cancer Group Trials Search Co-ordinator) in January 2014 and June 2015. As the updated search (Appendix 2) included amendments to the initial search strategy, we conducted a PubMed search from inception to June 2015 to ensure that no relevant articles had been missed. We compared the results of the overall PubMed search with the results of all other searches and examined any non-duplicate articles for possible inclusion in the review. We identified no relevant publications.

Searching other resources

We searched bibliographies of identified sources and use of Evidence Review Group (ERG) reports to the National Institute for Health and Care Excellence. We searched the proceedings of relevant conferences such as the American Society for Clinical Oncology and the European Society for Medical Oncology up to June 2015. If data were available, we considered including them in the review.

We developed a database of relevant references using EndNote X5 software (Thomson Reuters).

Data collection and analysis

Selection of studies

Two review authors independently took part in all stages of trial selection (FV and VB Search 1; VB and JG Search 2; JAG and YD, JAG and JG Search 3). Review authors first independently scanned the titles and abstracts of references identified by the search strategy. We obtained full details of possibly relevant trials and independently assessed these for inclusion in the review. In case of disagreement, the review authors attempted to reach consensus by discussion, or by involving a third review author (AB or JG). We excluded trials that did not meet all of the inclusion criteria and listed their bibliographic details with reasons for exclusion. We listed ongoing trials that did not report relevant data but met the inclusion criteria for future use. We included trials published in abstract form only if it was clear that the trial was eligible. If it was not clear, we contacted authors for further information and placed the trial in 'awaiting assessment' until we received a reply.

Data extraction and management

Two review authors carried out the data extraction (FV and VB Search 1; VB and JG Search 2; JAG and JG Search 3) using pre-tested data extraction forms, and a third review author (KD) independently checked the extracted data for accuracy. We extracted data relating to the outcome measures as well as information on trial design and participants (for example baseline characteristics). Where data from trials were presented in multiple publications, we extracted and reported these as a single trial with all other relevant publications listed.

Assessment of risk of bias in included studies

We assessed each included trial for risk of bias using criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (see domains listed below) (Higgins 2011). Two review authors (FV and JG Search 1; JG and KD Search 2) independently carried out the assessments. Any disagreements were resolved through discussion.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).
7. Any other identified bias, including inappropriate influence of funders.

We reported bias as either high, low, or unclear (further details of reporting bias are outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). We assessed the domains of blinding and incomplete outcome data at the outcome level.

We presented 'Summary of findings' tables with each outcome graded accordingly using the GRADE approach (GRADE Working Group 2004).

Measures of treatment effect

For binary outcomes, where sufficient data were available, we presented relative treatment effects in the form of risk ratio with 95% confidence intervals (CI). For continuous outcomes, we calculated mean differences and 95% CIs provided there was no evidence that the data were subject to skew. If statistical tests used in the original paper were for skewed data, or if median and interquartile ranges were reported, we assumed the data were skewed. We calculated standardised mean differences for quality of life variables where appropriate. For time-to-event outcomes, we extracted log hazard ratios (log HR) when available, with 95% CI. If the log HR was not reported, we requested data from authors.

All trials allowed participant cross-over to another treatment after progression, but no details were provided regarding how this was dealt with in any of the analyses of overall survival (OS).

We considered trials for inclusion in the review that: (1) provided only unplanned, interim findings; and (2) were continuing to recruit participants, but we did not not include these in the meta-analysis.

Unit of analysis issues

We did not include trials designed as cross-over trials, as the use of more than one treatment would impact on the assessment of OS (our primary outcome). However, we noted that many of the RCTs included in our review allowed participants from the control arm access to the intervention treatment when their disease progressed; we acknowledge that this limits our assessment of OS.

Dealing with missing data

We contacted authors (and sponsors) of trials for missing data. In cases where authors did not respond, we categorised the studies as 'awaiting classification'.

Assessment of heterogeneity

We assessed statistical heterogeneity between trials visually by inspection of the forest plots and using the Chi^2 test ($P < 0.1$ was considered significant due to the low power of the test). We also calculated the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Values of I^2 range from 0 to 100, with 0 representing no heterogeneity and 100 representing considerable heterogeneity.

For this review:

- 0% to 29%, heterogeneity might not be important;
- 30% to 49% may represent moderate heterogeneity;
- 50% to 74% may represent substantial heterogeneity; and
- 75% to 100%, considerable heterogeneity.

Assessment of reporting biases

If we identified a sufficient number of trials, we would construct a funnel plot. If asymmetry was present in the funnel plot, we would explore possible causes of bias, such as heterogeneity or outcome reporting bias. As there were not enough trials (at least 10) included in any one meta-analysis, we did not include funnel plots in this review.

Data synthesis

We have summarised individual trial data in structured tables and as a narrative description. As a major clinical issue is the toxicity of platinum-based doublet chemotherapy (cytotoxic chemotherapy), we presented subgroups separately with comparators cytotoxic chemotherapy, single-agent vinorelbine in elderly participants, and placebo. We regarded the combination of an EGFR-targeted therapy and cytotoxic chemotherapy versus cytotoxic chemotherapy as a separate comparison in view of concerns about interactions between chemotherapy and a tyrosine kinase inhibitor. We combined data for time-to-event outcomes using the generic inverse variance method. We used the Mantel-Haenszel method for dichotomous outcomes. In future versions of this review where data are available, we may combine continuous outcomes using the inverse variance method.

We conducted meta-analyses using the fixed-effect model, unless there was substantial heterogeneity ($I^2 > 50\%$), in which case we used a random-effects model as a sensitivity analysis. If there was considerable heterogeneity ($I^2 > 75\%$) we may have combined data, but our conclusions would highlight the amount of heterogeneity present.

Indirect comparisons and network meta-analysis

We considered that a network meta-analysis (NMA) was not appropriate because of the different populations across the included trials. We identified other barriers to conducting NMA: some trials reported adjusted analyses, whereas all other trials reported unadjusted analyses and combining these is statistically unsound; participants in all trials were allowed to switch treatment after progression, and we had no information about how this was handled in the analysis for OS. Finally, the Kaplan-Meier plots shown in the trial reports crossed in four of the trials, indicating that using a Cox proportional hazards model may not be appropriate.

If in future versions of this review we identify trials that compare different interventions that are sufficiently similar in terms of their populations and outcomes, we may make indirect comparisons for competing interventions that have not been compared directly. Multiple-treatments meta-analysis (also referred to as network meta-analysis) may combine direct and indirect comparisons using multivariate meta-analysis, as this will also take into account any multi-arm trials. We will use a random-effects model within STATA to conduct analyses using code from www.mtm.uoi.gr.

We will evaluate transitivity (the trials making different direct comparisons must be sufficiently similar in all respects other than the treatments being compared) clinically. We will compare the distributions of possible effect modifiers (smoking status, age, gender, ethnicity, and performance status) across comparisons using subgroup analysis. As the review only considers first-line treatment, indications are similar.

We will evaluate consistency using a loop-specific approach (Salanti 2009), and use a design interaction consistency model (Higgins 2012). If we identify inconsistency, we will not present the network meta-analysis.

We will assess estimates of treatment effect by pairwise meta-analysis. We will conduct network meta-analysis where appropriate.

Prior to analysis we will draw a diagram of the network for all relevant interventions, indicating the number of trials per comparison. We will derive and display ranking probabilities for each treatment using the Surface Under the Cumulative RAnking curve (SUCRA) plot and rankograms (Salanti 2011).

We will discuss the possible effects of risk of bias on the clinical effectiveness data and review findings.

Subgroup analysis and investigation of heterogeneity

In an update of this review when sufficient trials are included and where data are available, we may conduct analyses to investigate any differential effects in terms of:

- smoking status
- age
- sex
- ethnicity
- performance status
- type of mutation (exon 19/exon 21)
- type of histology

Sensitivity analysis

In an update of this review when sufficient trials are included, we will conduct sensitivity analyses based on the overall risk of bias of the included trials. We will base overall risk of bias on sequence generation, allocation concealment, and blinding (for the specific outcome), and will base the summary assessment on recommendations in Table 8.7a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

RESULTS

Description of studies

Results of the search

The database search strategy yielded 7674 non-duplicate papers. Of these, we screened 336 full-text records for inclusion in the review. We identified a further seven records via handsearching of reference lists and found two other records from our search of conference abstracts. We screened all of the potentially relevant references and included 19 eligible RCTs (reported in 56 publications) comparing EGFR-targeted therapy to chemotherapy as first-line treatment in NSCLC patients in our review (Figure 1).

Figure 1. Study flow diagram.

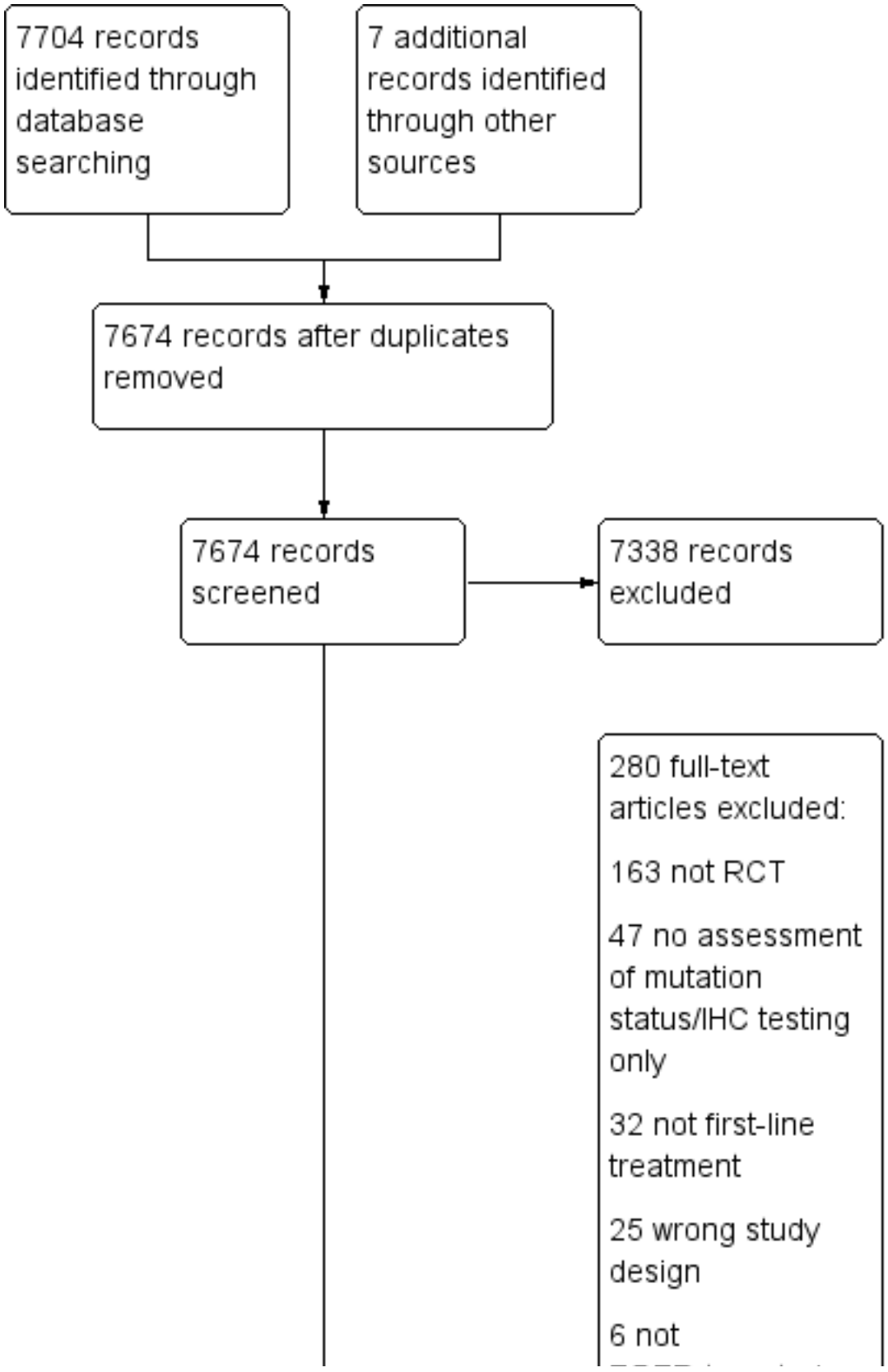
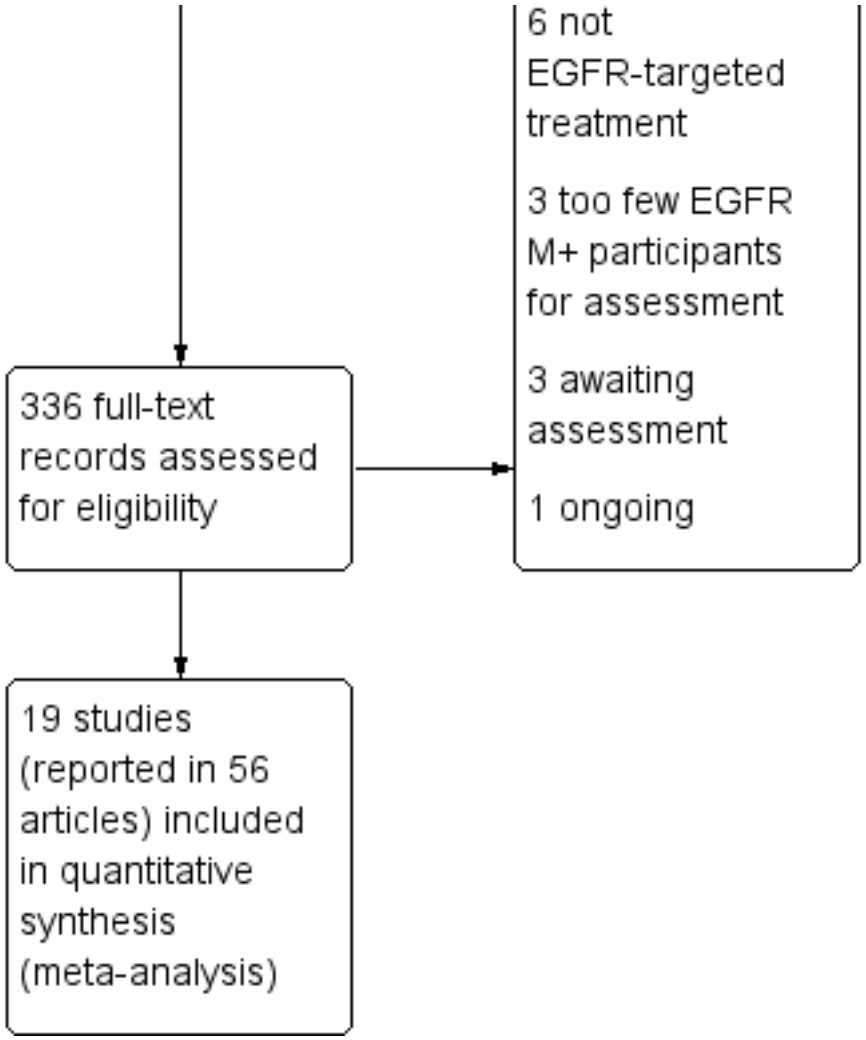


Figure 1. (Continued)



We classified three trials as awaiting assessment and have not yet included them in the review (INSPIRE; TALENT; TRIBUTE). We contacted the authors of TALENT and TRIBUTE and asked them to provide data on the EGFR M+ population. We have not received a response. We await the publication of outcomes for the EGFR M+ subgroup from INSPIRE. We found one ongoing trial (ARCHER).

Included studies

See Characteristics of included studies.

The 19 trials that met the inclusion criteria were published or updated between 2003 and 2015 (BMSO99; CHEN; ENSURE; EURTAC; FASTACT 2; First-SIGNAL; FLEX; GTOWG; INTACT 1; INTACT 2; IPASS; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; TOPICAL; TORCH; WJTOG3405; Yu 2014). With the exception of GTOWG, all trials were published as peer-reviewed papers. The overall number of people recruited to the trials ranged between 113, in CHEN, and 1217, in IPASS, with an overall trial population of 9414. The median length of follow-up (where reported) ranged from 15.9 months, in INTACT 1, to 59 months, in WJTOG3405.

Seven trials included EGFR M+ participants only (ENSURE; EURTAC; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405). The number of participants recruited to the EGFR M+ only trials ranged from 165, in OPTIMAL, to 364, in LUX-Lung 6, with a total population of 1672. The remaining 12 trials recruited a 'mixed' population of participants, that is participants were not selected for inclusion in the trial on the basis of their EGFR mutation status. These latter trials reported results for the subgroup of participants with EGFR M + mutation status. The numbers of participants reported in these subgroups ranged from 10, in GTOWG, to 261, in IPASS, with a combined total of 645. The combined total of participants with EGFR M+ NSCLC was 2317.

Three trials were conducted exclusively in Europe (EURTAC; GTOWG; TOPICAL); 10 were conducted exclusively in Asia (CHEN; ENSURE; FASTACT 2; First-SIGNAL; IPASS; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405; Yu 2014); and one was conducted in the USA (BMSO99). The remaining trials were more international, (TORCH), (INTACT 2). LUX-Lung 3, INTACT 1, and FLEX. The seven trials that recruited exclusively EGFR M+ patients were conducted in Asia, ENSURE, LUX-Lung 6, NEJSG, OPTIMAL, and WJTOG3405, and Europe, EURTAC, with one international trial (LUX-Lung 3).

Four of the trials were placebo controlled and double blinded (FASTACT 2; INTACT 1; INTACT 2; TOPICAL); the remainder were

specifically reported as being open label or did not report blinding status. In the latter case, we assumed these to be open label due to the nature of the interventions and comparator (that is oral versus intravenous treatments). Three of the 19 included trials were phase II (CHEN; GTOWG; Yu 2014), whilst the others were phase III. Fifteen of the 19 trials were partially or totally funded by a pharmaceutical company (BMSO99; CHEN; ENSURE; EURTAC; FASTACT 2; First-SIGNAL; FLEX; INTACT 1; INTACT 2; IPASS; LUX-Lung 3; LUX-Lung 6; OPTIMAL; TOPICAL; TORCH); the NEJSG and WJTOG3405 trials were funded by scientific groups. The funding source for the GTOWG and Yu 2014 trials was not reported.

Four categories of comparisons for all four agents were described:

1. targeted agent versus established platinum-based combinations (e.g. cisplatin or carboplatin and gemcitabine or docetaxel) - the term platinum-based refers to cisplatin or carboplatin based combinations, both drugs being metabolised to the same active moiety;
2. targeted agent versus single-agent chemotherapy drug vinorelbine, for which clinical interest is limited to the elderly population due to its favourable toxicity profile;
3. cytotoxic chemotherapy with the targeted agent versus chemotherapy alone; and
4. erlotinib versus placebo.

Population characteristics

All trials provided data for age, sex, performance status, and smoking status except for the INTACT 1, INTACT 2, and GTOWG trials (no details of smoking history). The median age of the overall population of all participants in the included trials ranged from 56 to 77 years; the median age of participants in the EGFR M+ only trials ranged from 56 to 65 years. Two trials only included people aged over 70 years (CHEN; GTOWG), and NEJSG and Yu 2014 only reported mean age. There were more females in nine trials (ENSURE; EURTAC; First-SIGNAL; IPASS; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405), and more males in seven trials (BMSO99; CHEN; FLEX; GTOWG; INTACT 1; INTACT 2; TORCH). The majority of participants were of good performance status (ECOG or WHO 0 or 1). The GTOWG abstract did not report performance status.

It is notable that in all of the trials that recruited EGFR M+ patients only, the proportion of females was greater than males (ENSURE; EURTAC; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405).

Interventions

Erlotinib

Eight trials used erlotinib (n = 754 EGFR M+) as the EGFR-targeted therapy (CHEN; ENSURE; EURTAC; FASTACT 2; GTOWG; OPTIMAL; TOPICAL; TORCH). CHEN and GTOWG used the drug vinorelbine as a single agent or with carboplatin, respectively, in elderly populations. In FASTACT 2, erlotinib was used in combination with a platinum doublet containing gemcitabine. We classified trials using erlotinib into the following comparison groups.

- Erlotinib versus platinum-based chemotherapy: One trial compared erlotinib versus gemcitabine plus carboplatin (OPTIMAL), two trials compared erlotinib versus gemcitabine plus cisplatin (ENSURE; TORCH), and one trial compared erlotinib versus docetaxel plus cisplatin or gemcitabine plus cisplatin (EURTAC).
- Erlotinib versus vinorelbine +/- chemotherapy: One trial compared erlotinib versus vinorelbine (CHEN), one trial compared erlotinib versus carboplatin plus vinorelbine (GTOWG).
- Erlotinib plus chemotherapy versus chemotherapy plus placebo: One trial compared erlotinib plus gemcitabine plus carboplatin or cisplatin versus gemcitabine plus carboplatin or cisplatin plus placebo (FASTACT 2).
- Erlotinib versus placebo: One trial considered this comparison (TOPICAL).

Gefitinib

Seven trials used gefitinib (n = 773 EGFR M+) as the EGFR-targeted therapy (First-SIGNAL; INTACT 1; INTACT 2; IPASS; NEJSG; WJTOG3405; Yu 2014). Three trials used gefitinib in combination with chemotherapy (INTACT 1; INTACT 2; Yu 2014). We classified trials using gefitinib into the following comparison groups.

- Gefitinib versus gemcitabine plus cisplatin: One trial considered this comparison (First-SIGNAL).
- Gefitinib versus paclitaxel plus carboplatin: Two trials considered this comparison (IPASS; NEJSG).
- Gefitinib versus docetaxel plus cisplatin: One trial considered this comparison (WJTOG3405).
- Gefitinib and carboplatin plus paclitaxel or cisplatin plus gemcitabine versus cytotoxic chemotherapy alone: Two trials considered this comparison (INTACT 1; INTACT 2). However, as EGFR M+ specific data from both trials was analysed as though from one trial, and data were only presented narratively.
- Gefitinib plus pemetrexed and cisplatin versus pemetrexed plus cisplatin: One trial considered this comparison (Yu 2014).

Afatinib

Two trials compared afatinib (n = 709) with cytotoxic chemotherapy (LUX-Lung 3; LUX-Lung 6). These trials differed principally in the selection of the cytotoxic chemotherapy comparator, LUX-Lung 3 comparing afatinib with cisplatin and pemetrexed in an ethnically diverse population, and LUX-Lung 6 comparing afatinib with cisplatin and gemcitabine in an Asian population. We combined these trials in a meta-analysis for progression-free survival, overall survival, and response.

Cetuximab

Two trials (n = 81) compared cetuximab plus chemotherapy with combination chemotherapy (BMSO99; FLEX).

Of the seven trials that recruited only people with EGFR M + NSCLC, two trials used afatinib (LUX-Lung 3; LUX-Lung 6), three used erlotinib (ENSURE: EURTAC; OPTIMAL), and two used gefitinib (NEJSG; WJTOG3405). All seven EGFR M+ only trials compared targeted treatment with cytotoxic chemotherapy (ENSURE; EURTAC; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405).

Outcomes

The primary outcome for the majority of trials was progression-free survival with secondary outcomes of overall survival, tumour response rate, symptom palliation, quality of life, and safety.

Overall survival was the primary outcome in six trials (First-SIGNAL; FLEX; INTACT 1; INTACT 2; TOPICAL; TORCH).

Excluded studies

See Characteristics of excluded studies.

We excluded 280 records after the selection procedure (Figure 1). The main reasons for exclusion were the use of non-randomised designs (including systematic reviews and reports from conferences), non-assessment of participants' EGFR mutation status, and non-administration of treatments as first-line therapy. We excluded other trials if they were designed to assess maintenance treatment, or if an EGFR-targeted therapy was used in both trial arms. We were unable to easily exclude articles at the screening stage, as we could not be certain from the abstract whether subgroup analyses of outcomes of participants with EGFR M+ tumours were reported. In the Characteristics of excluded studies table we have listed the 20 trials that appeared to meet the inclusion criteria, but on closer examination were not a complete match. Participants in five trials were not tested for EGFR mutations (Crino 2008; Gatzemeier 2003; Goss 2009; Lilenbaum 2008; Rosell 2004). Two trials tested for EGFR expression only (Rosell 2008; Thatcher 2014). Three trials included too few participants with EGFR M+ tumours to warrant analysis (FASTACT; Heigener 2014; White), and in eight trials tyrosine kinase inhibitors treatment was included in both trial arms (Hirsh 2011; Janne 2012; JO25567; Massuti 2014; NEJ005 2014; NEJ009; Xie 2015; Yang 2015). One trial only assessed outcomes of patients who had survived at one year (Boutsikou 2013), and in another trial there were insufficient samples available for testing (ECOG 4508).

Risk of bias in included studies

Allocation

Of the 19 included trials, 11 reported adequate information about the methods used to generate the randomisation sequence and the allocation concealment procedure; we considered these trials to be at low risk of bias (EURTAC; FASTACT 2; FLEX; IPASS; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; TOPICAL; TORCH; WJTOG3405). We considered the risk of bias for the remaining eight trials to be unclear due to lack of reported information (BMSO99; CHEN; ENSURE; First-SIGNAL; GTOWG; INTACT 1; INTACT 2; Yu 2014).

Blinding

Performance bias

Only 4 of the 19 included trials reported employing blinding procedures (INTACT 1; INTACT 2; NEJSG; TOPICAL). The remaining trials explicitly stated they were open label or did not report blinding status. In the latter case, we assumed these trials were open label due to the differences between interventions and comparator (that is oral versus intravenous).

Detection bias

We considered 11 of the trials to be at low risk of detection bias for the outcome of progression-free survival, as they incorporated independent verification procedures, in BMSO99, ENSURE, EURTAC, FASTACT 2, First-SIGNAL, LUX-Lung 3, LUX-Lung 6, and NEJSG, or blinded outcome assessment, in INTACT 1, INTACT 2, and TOPICAL. None of the remaining trials reported any independent assessment procedures and were considered to be at high risk of bias for the outcome of progression-free survival.

Incomplete outcome data

In all trials, all participants were accounted for in the analyses. There did not appear to be any major imbalances in drop-out rates between trial arms in any of the trials, therefore we considered all trials to be at low risk of bias.

Selective reporting

We considered only one trial to be at high risk of reporting bias (CHEN). The trial protocol stated time to progression as a secondary outcome of the trial, however the published paper did not report this outcome. We considered two trials to be at unclear risk of bias as the available information was insufficient to judge selective reporting (FLEX; GTOWG). We considered all other trials to be at a low risk of bias, as either trial protocols were available, or all outcomes stated in the methods section of the papers were reported.

Other potential sources of bias

Fifteen trials were sponsored fully or in part by pharmaceutical companies. One trial was terminated early as the non-inferiority of the intervention arm was demonstrated by the first planned interim analysis (TORCH). Two trials were terminated early for benefit (ENSURE; EURTAC).

Effects of interventions

See: **Summary of findings for the main comparison** Erlotinib vs control; **Summary of findings 2** Gefitinib vs paclitaxel + carboplatin; **Summary of findings 3** Afatinib vs chemotherapy

Pairwise meta-analysis

Erlotinib versus placebo, platinum-based chemotherapy, or other cytotoxic agents

Primary outcome: Overall survival

Data from five trials were available for overall survival (OS) (CHEN; ENSURE; EURTAC; FASTACT 2; TORCH). Three trials presented limited data (OPTIMAL; TOPICAL), and one trial presented no data (GTOWG).

Erlotinib versus platinum-based chemotherapy: The pooled treatment effect estimate for three trials, hazard ratio (HR) of 0.95 (95% confidence interval (CI) 0.75 to 1.22; $I^2 = 0$; 71%) indicated no significant difference in OS between the groups (ENSURE; EURTAC; TORCH). OPTIMAL reported that OS did not differ significantly between the two treatment arms (HR = 1.065, P = 0.6849). No standard error was reported, so the results could not be entered into a meta-analysis.

Erlotinib versus vinorelbine: CHEN reported a HR of 2.16 (95% CI 0.58 to 8.10) for OS comparing erlotinib versus vinorelbine in elderly patients, indicating no significant difference in OS between the groups.

Erlotinib plus cytotoxic chemotherapy versus cytotoxic chemotherapy plus placebo: FASTACT 2 reported a HR of 0.48 (95% CI 0.27 to 0.85) for OS indicating a significant difference in OS favouring erlotinib plus cytotoxic chemotherapy in a trial of 91 participants (Analysis 1.1).

Erlotinib versus placebo: TOPICAL reported the median overall survival, which was 10.4 months (95% CI 5.5 to 15.1) for erlotinib (n = 17) versus 3.7 months (95% CI 0.3 to 49.3) for placebo (n = 11).

Secondary outcomes

1. Progression-free survival

Six trials reported progression-free survival (PFS) (CHEN; ENSURE; EURTAC; FASTACT 2; OPTIMAL; TORCH). One trial did not report hazard ratios and only presented limited data (TOPICAL), and one trial reported no data (GTOWG).

Erlotinib versus chemotherapy: The pooled treatment effect estimate for four trials (HR 0.30, 95% CI 0.24 to 0.38; fixed-effect; I^2 = 74%) favoured erlotinib (ENSURE; EURTAC; OPTIMAL; TORCH). As there was a substantial amount of heterogeneity, we performed a sensitivity analysis using the random-effects model, and results were similar to the main analysis (HR 0.31, 95% CI 0.20 to 0.50).

Erlotinib versus vinorelbine: CHEN reported a HR of 0.55 (95% CI 0.21 to 1.46) for PFS indicating no significant difference between the groups.

Erlotinib plus cytotoxic chemotherapy versus cytotoxic chemotherapy plus placebo: FASTACT 2 reported a significant difference in PFS favouring erlotinib plus cytotoxic chemotherapy (HR 0.25, 95% CI 0.16 to 0.39) (Analysis 1.2).

Erlotinib versus placebo: TOPICAL reported the median PFS, which was 4.8 months (95% CI 1.6 to 8.8) for erlotinib (n = 17) and 2.9 months (95% CI 0.3 to 10.1) for placebo (n = 11).

ENSURE, EURTAC, and OPTIMAL showed an improvement in PFS for the exon 19 deletion in favour of erlotinib. We did not perform meta-analysis of this preliminary data.

2. Tumour response

Erlotinib versus platinum-based chemotherapy: The pooled treatment effect estimate for five trials favoured erlotinib (risk ratio (RR) 2.26, 95% CI 1.85 to 2.76; I^2 = 57%) (ENSURE; EURTAC; GTOWG; OPTIMAL; TORCH). As there was a substantial amount of heterogeneity, we performed a sensitivity analysis using a random-effects model, and results were similar (RR 2.20, 95% CI 1.53 to 3.17) (Analysis 1.3).

Erlotinib versus vinorelbine: CHEN reported a RR of 0.83 (95% CI 0.19 to 3.67; 24 participants) for tumour response, indicating no significant differences in tumour response between the groups.

FASTACT 2 observed an objective response in 41 (84%) of 49 participants with EGFR-activating mutations in the erlotinib plus cytotoxic chemotherapy group, and 7 (15%) of 48 participants in the chemotherapy plus placebo group (RR 5.74, 95% CI 2.86 to 11.50).

TOPICAL did not report tumour response for EGFR M+ participants.

3. Toxicity and adverse effects of treatment.

The most commonly reported adverse effects of treatment (AEs) in participants treated with erlotinib as a monotherapy were rash, diarrhoea, and fatigue (CHEN; ENSURE; EURTAC; GTOWG; OPTIMAL; TOPICAL; TORCH) (Table 1). Other AEs included mouth ulcers, constitutional symptoms, nausea, increased alanine aminotransferase , dyspnoea, and pulmonary toxicities. Cytotoxic chemotherapy was associated with greater grade 3/4 myelosuppression, fatigue (two trials) and anorexia (one trial). Commonly reported AEs in the trial that administered erlotinib in combination with cytotoxic chemotherapy were neutropenia, thrombocytopenia, and anorexia (FASTACT 2).

4. Quality of life

Two trials reported on the quality of life (QoL) of EGFR M+ participants (OPTIMAL; TORCH). One trial used the Lung Cancer Symptom Scale (LCSS) to measure QoL, but compliance was so poor that the authors regarded the analysis as inconclusive (EURTAC).

QoL was measured but not reported in the trial reports in GTOWG, and was not available for the EGFR M+ subgroup in three trials (CHEN; FASTACT 2; TOPICAL).

TORCH used the the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30) and the lung cancer-specific module (EORTC QLQ-LC13) to evaluate QoL. The number of participants improved/stable/worse was reported for selected and unselected participants receiving erlotinib and chemotherapy. Improvement in terms of global QoL and physical functioning was particularly evident in the small numbers of EGFR M+ participants (n = 36/39 available for analysis) for erlotinib compared to cytotoxic chemotherapy.

OPTIMAL used the Functional Assessment of Cancer Therapy-Lung (FACT-L), LCSS, and Trial Outcome Index (TOI) to assess QoL. The odds ratios (ORs) (with covariates EGFR mutation type, smoking history, and histological type) were in favour of erlotinib and were 6.69 (95% CI 3.01 to 14.85; P = 0.0001), 7.54 (95% CI 3.38 to 16.85; P = 0.0001), and 8.07 (95% CI 3.57 to 18.26; P = 0.0001), respectively.

In the ENSURE trial, deterioration in TOI was 11.4 months for erlotinib compared to 4.2 months for chemotherapy (HR 0.51, 95% CI 0.34 to 0.76; P = 0.0006), and time to deterioration in QoL was 8.2 months for erlotinib compared to 2.8 months for chemotherapy (HR 0.64, 95% CI 0.44 to 0.93; P = 0.0168).

5. Symptom palliation

In the TORCH trial, the time to deterioration curves for cough, dyspnoea, and pain in the first 20 weeks were visually assessed for erlotinib versus chemotherapy, and no major differences were observed. No statistical analyses were provided by the authors.

The OPTIMAL trial reported that the time to improvement of symptoms on the FACT-L, TOI, and LCSS (sometimes abbreviated to Lung Cancer Subscale (LCSS)) was significantly shorter for erlotinib compared to chemotherapy: FACT-L 1.51 versus 3.19 months (P = 0.0067); TOI 2.79 versus 3.48 months (P = 0.003); LCSS 1.48 versus 3.15 months (P = 0.0010). There was also significant correlation between overall response and improvement in symptom scores (P = 0.0006, 0.0002, and 0.0213 for FACT-L, TOI, and LCSS, respectively).

In the ENSURE trial, preliminary data using the FACT-L showed that time to symptomatic progression was 13.8 months for erlotinib compared to 5.5 months for chemotherapy (HR 0.56, 95% CI 0.36 to 0.87; P = 0.0076).

Gefitinib versus cytotoxic chemotherapy

Primary outcome: Overall survival

We could not combine data for all four trials comparing gefitinib to platinum-based chemotherapy (First-SIGNAL; IPASS; NEJSG; WJTOG3405), as two trials reported only adjusted analyses (IPASS; NEJSG). It is not advisable to combine adjusted and unadjusted estimates.

Gefitinib versus gemcitabine plus cisplatin: One trial, First-SIGNAL, reported a HR of 1.04 (95% CI 0.50 to 2.20)

Gefitinib versus carboplatin and paclitaxel: Pooled analysis of the two trials indicated no significant difference in OS between the groups (HR 0.95, 95% CI 0.77 to 1.18; $I^2 = 0$) (IPASS; NEJSG).

Gefitinib versus docetaxel plus cisplatin: WJTOG3405 reported a HR of 1.25 (95% CI 0.88 to 1.78), indicating no significant difference in OS between the groups (Analysis 2.1).

Gefitinib and platinum-based chemotherapy versus platinum-based chemotherapy. INTACT 1 and INTACT 2 reported a combined HR of 1.77 (95% CI 0.50 to 6.23), indicating no significant difference in OS between the groups. Yu 2014 did not report on OS.

Secondary outcomes

1. Progression-free survival

Gefitinib versus gemcitabine plus cisplatin: First-SIGNAL reported a HR of 0.54 (95% CI 0.27 to 1.10), indicating no significant difference in PFS between the groups.

Gefitinib versus paclitaxel plus carboplatin: The pooled treatment effect estimate for two trials showed a significant difference in PFS between the groups, favouring gefitinib (HR 0.39, 95% CI 0.32 to 0.48; $I^2 = 73\%$) (IPASS; NEJSG). As there was a substantial amount of heterogeneity, we performed a sensitivity analysis using a random-effects model, and results were similar (HR 0.39, 95% CI 0.26 to 0.59).

Gefitinib versus docetaxel plus cisplatin: WJTOG3405 reported a significant difference in PFS favouring gefitinib (HR 0.49, 95% CI 0.34 to 0.71) (Analysis 2.2).

Gefitinib and cytotoxic chemotherapy versus cytotoxic chemotherapy: INTACT 1 and INTACT 2 reported a HR of 0.55 (95% CI 0.19 to 1.60), indicating no significant difference in PFS between the groups in a combined total of 32 participants.

Yu 2014 reported a HR of 0.20 (95% CI 0.05 to 0.75) for PFS for comparison of gefitinib plus pemetrexed and cisplatin vs pemetrexed plus cisplatin.

IPASS and NEJSG both showed an improvement in PFS for the exon 19 deletion in the gefitinib population.

2. Tumour response

The pooled treatment effect estimate for four trials, First-SIGNAL, IPASS, NEJSG, and WJTOG3405, favoured gefitinib (RR 1.87, 95% CI 1.60 to 2.19; $I^2 = 58\%$) (Analysis 2.3). As there was a substantial amount of heterogeneity, we performed a sensitivity analysis using a random-effects model, and results were similar (RR 1.92, 95% CI 1.46 to 2.52).

INTACT 1 and INTACT 2 showed the response rates for gefitinib plus cytotoxic chemotherapy were the same as for cytotoxic chemotherapy alone (30.4% versus 28.7%). Yu 2014 reported a response rate of 77% for cytotoxic chemotherapy plus gefitinib compared to cytotoxic chemotherapy alone (P = 0.13).

Response at cross-over after progression on first-line treatment

NEJSG reported that 28.2% of 52 participants responded to carboplatin and paclitaxel after progressing on gefitinib, and 58.5% of 106 participants responded to gefitinib after progressing on carboplatin and paclitaxel.

INTACT 1 and INTACT 2 reported that 13 out of 18 (72%) of EGFR M + participants responded to gefitinib plus cytotoxic chemotherapy, while 2 out of 5 (40%) of EGFR M+ participants responded to cytotoxic chemotherapy alone.

3. Toxicity and adverse effects of treatment

The most commonly reported AE for gefitinib monotherapy was rash, followed by liver toxicity, anorexia, and diarrhoea (First-SIGNAL; IPASS; NEJSG; WJTOG3405) (Table 1). Cytoxic chemotherapy was associated with greater grade 3/4 myelosuppression in all comparisons and greater anorexia in one trial. The commonly reported AEs for gefitinib plus cytotoxic chemotherapy were thrombocytopenia, rash, diarrhoea and neutropenia (INTACT 1; INTACT 2).

4. Quality of life

Two trials reported on QoL (IPASS; NEJSG). QoL was measured but not reported in the trial reports in one trial (INTACT 2), not measured in two trials (INTACT 1; WJTOG3405), and not available for the EGFR M+ subgroup in one trial (First-SIGNAL).

IPASS used the FACT-L and TOI symptom improvement by the LCSS and achieved 89.5% compliance for the cytotoxic chemotherapy group and 94.8% for the gefitinib group. Gefitinib was significantly favoured over carboplatin plus paclitaxel in the proportion of participants showing improvement in FACT-L total score, TOI, and LCSS (FACT-L total score 70.2% versus 44.5% (OR 3.01, 95% CI 1.79 to 5.07), TOI 70.2% versus 38.3% (OR 3.96, 95% CI 2.33 to 6.71), LCSS 75.6% versus 53.9% (OR 2.70, 95% CI 1.58 to 4.62)). The time-to-deterioration data showed a median of 15.6 months for gefitinib compared to 3.0 months for cytotoxic chemotherapy for FACT-L; 16.6 months for gefitinib compared to 2.9 months for cytotoxic chemotherapy for TOI; and 11.3 months for gefitinib compared to 2.9 months for cytotoxic chemotherapy for LCSS. In the 131 participants in the gefitinib group who improved, the median time to improvement in all three scores was either 8 or 11 days.

NEJSG assessed QoL weekly using the Care Notebook and achieved compliance in 72 participants (63%) on chemotherapy and 76 participants (69%) on gefitinib. They used three categories of physical, mental, and "life" well-being, each of which had three subcategories. The number of participants improved/stable/worse was also reported, and there was no difference between the treatment arms in mental well-being. However, the physical and life scales were all better for gefitinib than for cytotoxic chemotherapy. The data for daily functioning was quoted as HR 0.32 (95% CI 0.17 to 0.59; P<0001).

5. Symptom palliation

In the NEJSG trial, participants who received gefitinib had a significantly longer time to deterioration up to 20 weeks than participants who received paclitaxel plus carboplatin using both 9.1% and 27.3% levels of deterioration. The data for 27.3% deterioration for pain and shortness of breath showed HR 0.28 (95% CI 0.17 to 0.46; P = 0.0001) in favour of gefitinib.

Afatinib versus cisplatin-based chemotherapy

Afatinib versus pemetrexed plus cisplatin: One trial considered this comparison (LUX-Lung 3).

Afatinib versus gemcitabine plus cisplatin: One trial considered this comparison (LUX-Lung 6).

Primary outcome: Overall survival

The pooled treatment effect estimate indicated no significant difference in OS between the groups (HR 0.93, 95% CI 0.74 to 1.17; I^2 = 0; 2 trials) (Analysis 3.1), although data for LUX-Lung 6 were immature. A preliminary report of a pooled analysis of participants with an exon 19 deletion or L858R mutation showed improved survival for afatinib compared to cytotoxic chemotherapy in participants with an exon 19 deletion (HR 0.81, 95% CI 0.66 to 0.99; P= 0.037) (Yang 2014). We did not formally assess analysis of mutation site in this review.

Secondary outcomes

1. Progression-free survival

The pooled treatment effect estimate showed a significant difference in PFS between the groups favouring afatinib (HR 0.42, 95% CI 0.34 to 0.53; I^2 = 90%; 2 trials) (Analysis 3.2). As there was a substantial amount of heterogeneity, we performed a sensitivity analysis using a random-effects model, and results were similar (HR 0.41, 95% CI 0.20 to 0.83).

2. Tumour response

The pooled treatment effect estimate favoured afatinib (RR 2.71, 95% CI 2.12 to 3.46; I^2 = 0%; 2 trials) (Analysis 3.3).

3. Toxicity and adverse effects of treatment

The most commonly reported grade 3/4 AEs in the afatinib-treated participants were rash and diarrhoea, paronychia, and stomatitis/mucositis (LUX-Lung 3; LUX-Lung 6) (Table 1). Myelosuppression was consistently greater in the chemotherapy arms, while greater fatigue was seen in one comparison. Diarrhoea was worse with afatinib in both trials.

4. Quality of life

In LUX-Lung 3, improvement was noted using the EORTC QLQ-C30 scale in global health, physical, cognitive, and role function in favour of afatinib over cisplatin plus pemetrexed chemotherapy.

LUX-Lung 6 also used the EORTC QLQ-C30 scale and the lung cancer-specific module QLQ-LC13 with greater than 90% compliance. A greater percentage of participants showed improvement in global health scores/QoL scores (P < 0.0001), physical function (P < 0.0001), and social function (P < 0.0001) with afatinib when compared to cisplatin plus gemcitabine. Subgroup analysis showed delay in time to deterioration in cough, dyspnoea, and pain.

5. Symptom palliation

In the LUX-Lung 3 trial, time-to-deterioration curves for cough and dyspnoea showed a significant effect in favour of afatinib (HR 0.60, 95% CI 0.41 to 0.87; P = 0.007) and (HR 0.68, 95% CI 0.50 to 0.93; P = 0.02), respectively. The HR for pain 0.83 (95% CI 0.62 to 1.10) was not statistically significant (P = 0.19).

In the LUX-Lung 6 trial, time to deterioration for cough (HR 0.45; P = 0.0003), dyspnoea (HR 0.54; P < 0.0001), and pain (HR 0.70; P = 0.003) showed a significant effect in favour of afatinib (HR 0.56, 95% CI 0.41 to 0.77; P = 0.0002).

Cetuximab plus cytotoxic chemotherapy versus cytotoxic chemotherapy

Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin: One trial considered this comparison (BMSO99).

Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin: One trial considered this comparison (FLEX).

Primary outcome: Overall survival

We could not pool data for the two trials comparing cetuximab plus cytotoxic chemotherapy to cytotoxic chemotherapy, as one trial reported only an adjusted analysis (FLEX).

BMSO99 reported a HR of 1.62 (95% CI 0.54 to 4.84), indicating no significant difference in OS between the groups (Analysis 4.1).

FLEX reported a HR of 1.48 (95% CI 0.77 to 2.82), indicating no significant difference in OS between the groups (Analysis 4.1).

Secondary outcomes

1. Progression-free survival

We could not pool data for the two trials comparing cetuximab plus cytotoxic chemotherapy to cytotoxic chemotherapy, as one trial reported only an adjusted analysis (FLEX).

BMSO99 reported a HR of 1.17 (95% CI 0.36 to 3.80), indicating no significant difference in PFS between the groups (Analysis 4.2).

FLEX reported a HR of 0.92 (95% CI 0.53 to 1.60), indicating no significant difference in PFS between the groups (Analysis 4.2).

2. Tumour response

The pooled treatment effect estimate (RR 1.43, 95% CI 0.83 to 2.47; I^2 = 40%; 2 trials) indicated no significant difference between the groups (Analysis 4.3).

3. Toxicity and adverse effects of treatment

The most commonly reported AEs in the cetuximab-treated participants were neutropenia, leukopenia, febrile neutropenia, and fatigue (BMSO99; FLEX) (Table 1).

4. Quality of life

FLEX used the EORTC QLQ-C30 and LCSS, and found no difference in QoL between the groups.

QoL was not available for the EGFR M+ subgroup in BMSO99.

5. Symptom palliation

Neither trial reported specifically on symptom palliation.

Toxicity and adverse effects of treatment - general comments

The reporting of AEs differed across the 19 included trials. We described in Table 1 the trial-defined reporting of AEs, and tabulated the three most frequently occurring grade 3 or 4 AE for both the intervention and comparator arms of each trial. The data reported were for overall trial populations, and therefore include non-EGFR M+ participants in trials where these were unselected. The trials are grouped according to the EGFR-targeted treatment employed (erlotinib, gefitinib, afatinib, cetuximab).

LUX-Lung 3 and LUX-Lung 6 reported three and two participants with interstitial lung disease, respectively (1%) in the afatinib arms.

The AEs associated with cytotoxic chemotherapy in all comparisons were neutropenia, fatigue, leukopenia, vomiting, anaemia, decreased appetite, diarrhoea, anorexia, thrombocytopenia, arthralgia, neuropathy, and dyspnoea.

Assessment of reporting biases

We have not included a funnel plot in the current review as we did not include a sufficient number of trials (n = 10) in any meta-analysis. However, we devised and carried out a thorough search strategy to reduce the impact of publication bias.

Subgroup analyses

We did not include sufficient trials to allow subgroup analyses of smoking history, age, sex, ethnicity, type of mutation, or performance status.

Sensitivity analyses

We did not include sufficient trials in any one meta-analysis to allow us to undertake the sensitivity analyses specified in the Methods section. However, where we detected moderate heterogeneity, we used a random-effects model as a sensitivity analysis to compare results with the fixed-effect model. We have reported these in the Effects of interventions section.

Network meta-analysis

We considered that network meta-analysis was not appropriate because of the different populations aross the included trials. We identified other barriers to conducting network meta-analysis: two trials reported adjusted analyses (IPASS; NEJSG), whereas all other trials reported unadjusted analyses; participants in all trials were allowed to switch treatment after progression, and we had no information regarding how this was handled in the analysis for OS; and finally, the Kaplan-Meier plots shown in the trial reports crossed in four trials, indicating that using a Cox proportional hazards model may not be appropriate.

Summary of findings table

We have presented tables for pooled analyses for the outcomes of OS and PFS: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

DISCUSSION

Summary of main results

This review included 19 RCTs with a combined total of 2317 participants with EGFR M+ NSCLC. We identified four EGFR-targeted treatments: erlotinib (eight trials); gefitinib (seven trials); afatinib (two trials); and cetuximab (two trials). We did not consider network meta-analysis to be appropriate because of the different populations of included trials, the reporting of adjusted analyses versus unadjusted analyses, and the inappropriate use of the Cox proportional hazards model in some trials.

Our primary endpoint was overall survival (OS), and only one small (N = 97) trial reported a statistically significant OS gain (for participants treated with erlotinib plus cytotoxic chemotherapy versus cytotoxic chemotherapy alone) (FASTACT 2). None of the remaining 18 included trials demonstrated any OS benefit of targeted therapy compared with cytotoxic chemotherapy. No OS effect was demonstrated in pooled analyses of erlotinib in ENSURE, EURTAC, and OPTIMAL. Pooled analysis of two gefitinib trials, IPASS and NEJSG, and the two afatinib trials, LUX-Lung 3 and LUX-Lung 6, also showed no OS benefit. It is important to note that the majority of the included trials of anti-EGFR monotherapy allowed participants to switch treatments on disease progression, which will have a confounding effect on any OS analysis.

For the secondary endpoint of progression-free survival (PFS), a pooled analysis of four trials of erlotinib demonstrated a statistically significant benefit compared with cytotoxic chemotherapy (HR 0.30, 95% CI 0.24 to 0.38; 595 participants) (ENSURE; EURTAC; OPTIMAL; TORCH). Of the non-pooled trials, for erlotinib versus cytotoxic chemotherapy, CHEN reported a non-significant PFS effect of erlotinib (n = 24), and FASTACT 2 (n = 97) reported a significant PFS benefit for erlotinib (HR 0.25, 95% CI 0.16 to 0.39). The pooled analysis of gefitinib trials IPASS and NEJSG (N = 491) demonstrated a significant benefit of gefitinib compared with paclitaxel with carboplatin (HR 0.39, 95% CI 0.32 to 0.48). A single trial, WJTOG3405, also demonstrated a significant difference in PFS favouring gefitinib (HR 0.49, 95% CI 0.34 to 0.71). One other trial, First-SIGNAL, demonstrated no statistically significant benefit of gefitinib compared with gemcitabine plus cisplatin (n = 42). The remaining two trials that featured gefitinib, INTACT 1 and INTACT 2, reported no difference between a regimen of gefitinib plus cytotoxic chemotherapy compared with cytotoxic chemotherapy plus placebo (n = 32). Heterogeneity was high in the pooled analyses of both erlotinib and gefitinib. Five trials showed a significant improvement in PFS for the tyrosine-kinase inhibitor (TKI) in tumours harbouring the Del19 mutation compared to chemotherapy (EURTAC; IPASS; LUX-Lung 3; NEJSG; OPTIMAL). We have not performed meta-analysis of this mutation site-specific data.

In the analysis of tumour response, a pooled analysis of 4 trials of erlotinib including 387 participants favoured treatment with erlotinib (RR 2.57, 95% CI 1.97 to 3.34) (EURTAC; GTOWG; OPTIMAL; TORCH). One trial of erlotinib plus cytotoxic chemotherapy (n = 97) also favoured treatment with erlotinib (FASTACT 2), whilst one other small trial of erlotinib versus cytotoxic chemotherapy reported no benefit of erlotinib (n = 24) (CHEN). For gefitinib, all 7 trials demonstrated a statistically significant benefit for gefitinib compared to cytotoxic chemotherapy: a pooled analysis of 4 trials including 648 participants yielded a RR of 1.87 (95% CI 1.60 to 2.19)

(First-SIGNAL; IPASS; NEJSG; WJTOG3405). Both afatinib trials (n = 709) reported a statistically significant benefit of afatinib compared with cytotoxic chemotherapy (LUX-Lung 3; LUX-Lung 6); the pooled analysis yielded a RR of 2.71 (95% CI 2.12 to 3.46). As for the PFS analyses, heterogeneity was high for the erlotinib and gefitinib pooled comparisons and low for the two afatinib trials. No benefit for cetuximab was reported for either trial (BMSO99; FLEX).

The most commonly reported adverse effects (AEs) for people treated with TKI monotherapy were rash, diarrhoea, paronychia, stomatitis/mucositis (afatinib), and rash, diarrhoea, and fatigue (erlotinib and gefitinib). These AEs are consistent with those listed in the Summary of Product Characteristics for these products, which include diarrhoea, rash, interstitial lung disease, liver impairment, and ocular disorders. Participants treated with cytotoxic chemotherapy experienced the AEs usually associated with this treatment, for example neutropenia, febrile neutropenia, leukopenia, and fatigue. However, it was difficult to accurately characterise and compare AEs across trials due to the different methods of reporting (definitions used and styles of reporting). This is particularly relevant to the rare but serious AE of interstitial lung disease. A recent meta-analysis of erlotinib and gefitinib trials reported an incidence of 1.2% for interstitial lung disease with a mortality rate of 22.8% (Shi 2014). The data presented for afatinib suggest this complication occurs with equal frequency in all three TKIs, although no data on duration of therapy was provided. In addition, it should be noted that the AEs reported are relevant to an overall trial population, and in the 12 trials where EGFR M+ status was not an inclusion criterion, are drawn from a much larger population. However, our comparisons highlight the differences in the AEs associated with TKIs and cytotoxic chemotherapy (Pilkington 2012).

Six trials measured quality of life for participants with EGFR M + tumours by a number of different methods (two comparing afatinib with cytotoxic chemotherapy, two comparing erlotinib with cytotoxic chemotherapy, and two comparing gefitinib with cytotoxic chemotherapy); all six trials reported a beneficial effect of the TKI compared to cytotoxic chemotherapy. All three TKIs showed symptom palliation of cough, pain, and dyspnoea, although the methodology used was not standardised.

Any benefit in survival has to be weighed against increased toxicity. The median number of chemotherapy cycles given in the control arms was four out of a planned six three-weekly cycles. The oral agents were generally given until progression and appeared to be better tolerated. The median duration of therapy was estimated to be around 9 to 12 months. In the two gefitinib trials where data were presented, the number of participants discontinuing therapy was similar in the two groups, while in the EURTAC trial a higher proportion of participants on chemotherapy than on erlotinib discontinued due to toxicity.

Overall completeness and applicability of evidence

Median survival of people with advanced stages III, IV NSCLC is on the order of 12 months, and for adenocarcinomas 18 months. At present, there is no indication that increases in PFS fully translate into OS benefit, which is consistent with the evidence in the current literature base (Booth 2012). However, there was wide variation in the selection criteria for the included trials, including age, sex, smoking, and EGFR sequencing method. The later trials recruited participants only with proven EGFR mutations, and saw longer survival times. However, with the comparatively short survival in NSCLC, AEs and quality of life for either first-line or second-line treatments are important. The interpretation of OS was limited by cross-over in most trials. From the limited data available on cross-over at disease progression, the targeted agents and cytotoxics would appear to act on different cell populations.

Mutations in EGFR can be assessed by several methods including direct sequencing of the tumours, circulating tumour cells (Maheswaran 2008), or cell-free DNA (Bai 2013). Firstly, heterogeneity in the proportion of malignant and normal/stromal cells in the tissues sampled may contribute to variation in the classification of tumours as EGFR M+ or EGFR wild type based on the location of the sample, as in the majority of trials in this review (Tsiatis 2010), and there is preliminary evidence of heterogeneity of mutation analysis with multiple tissue sampling (Bai 2013). Secondly, methodological issues in the assessment of EGFR mutations may contribute to false-negative results (Vogelstein 2013). We excluded immunohistochemical-only categorisation of mutation from this review.

Data on the types of mutations in relation to their sensitivity to targeted therapy is limited (EURTAC). Of the three common sites of mutation, there is evidence that tumours with codon 20 mutations are resistant to EGFR TKI, while tumours with exon 19 or L858R codon 21 mutations are sensitive to EGFR TKI (Yasuda 2011). The improved survival of exon 19 deletion patients with afatinib compared to cytotoxic chemotherapy suggests that further data will evolve based on more detailed molecular characterisation of EGFR M+ NSCLC (Yang 2014). The cetuximab trials assessed K-RAS and HER-2 mutations and demonstrated no predictive effect of the biomarkers (Linardou 2008). Non-randomised trials have shown that some mutations, principally T790M in codon 20, may contribute to the development of acquired resistance to these agents (Kosaka 2006; Rosell 2011; Su 2012). Some trials did not include assessment of exons 18 and 20 mutations, although only four of the included trials excluded T790M mutations (FLEX; LUX-Lung 3; LUX-Lung 6; NEJSG).

With improving data on individualisation of treatment according to morphological and molecular criteria, patient choice may be a factor in the decision to accept significant toxicity (for example from cytotoxic chemotherapy) at an earlier or later stage of NSCLC management. This review provides strong data supporting first-line EGFR TKI in people where EGFR mutation status is known to be positive. As mutation testing is not universally available, and the response time of reporting can be prolonged, chemotherapy may be an acceptable first-line option when histological subtype and smoking history are known in patients with good performance status. Quality control of mutation profiling methodology and international agreement on standardisation would improve confidence in the use of EGFR TKIs in EGFR M+ patients.

There is some published evidence of ethnic differences in platinum-based haematological toxicity, with Asian patients having a higher incidence of grade 3/4 neutropenia compared to non-Asian patients, based on a pooled analysis of 11,271 participants in 50 phase II and III trials (Hasegawa 2011). It is less well established if there are ethnic differences in response to targeted therapies in the EGFR M+ subgroup, and there was wide variation in the ethnic composition of the reported trials. The majority of the data came from Asian patients, whose tumours may differ in genetic

composition, both inherited and that acquired from carcinogen exposure, from non-Asian patients.

Quality of the evidence

All the included trials were randomised, and the overall number of participants (n = 2317) in the 19 trials provides reasonable power to support the conclusions. The participants were spread across four different drug treatments (erlotinib, gefitinib, afatinib, and cetuximab), reducing the number providing data for each treatment.

We considered the quality of the evidence to be high for all comparisons (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). With the exception of FASTACT 2, all trials were of an open-label design, however all but one trial, IPASS, reported independent review of radiographic outcomes.

The 'Risk of bias' table indicates a mixed risk of bias across the included trials for the majority of the assessment criteria, with most trials at unclear or high risk of bias (Figure 2; Figure 3). The two items considered to be at high risk of bias across the trials were related to blinding of treatment allocation for participants and personnel and blinding of outcome assessment. Blinding of participants and administrators is difficult to achieve in trials that compare oral therapy with intravenous chemotherapy treatments, and even if blinding procedures are implemented, the appearance of a rash (a common side effect of treatment with a TKI) would indicate the treatment regimen used. FASTACT 2 was blinded in both treatment allocation and imaging assessment. Blinding of outcome assessment is important when time-to-treatment-failure outcomes, such as PFS, are the indicators of treatment efficacy, and blinded outcome assessment or blinded review of assessment should be part of the trial protocol. Of the large industry-funded trials, OPTIMAL did not report blinding of outcome assessment for erlotinib, and neither did IPASS or WJTOG3405 for gefitinib. We acknowledge that some trials may have implemented such procedures but did not report them.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

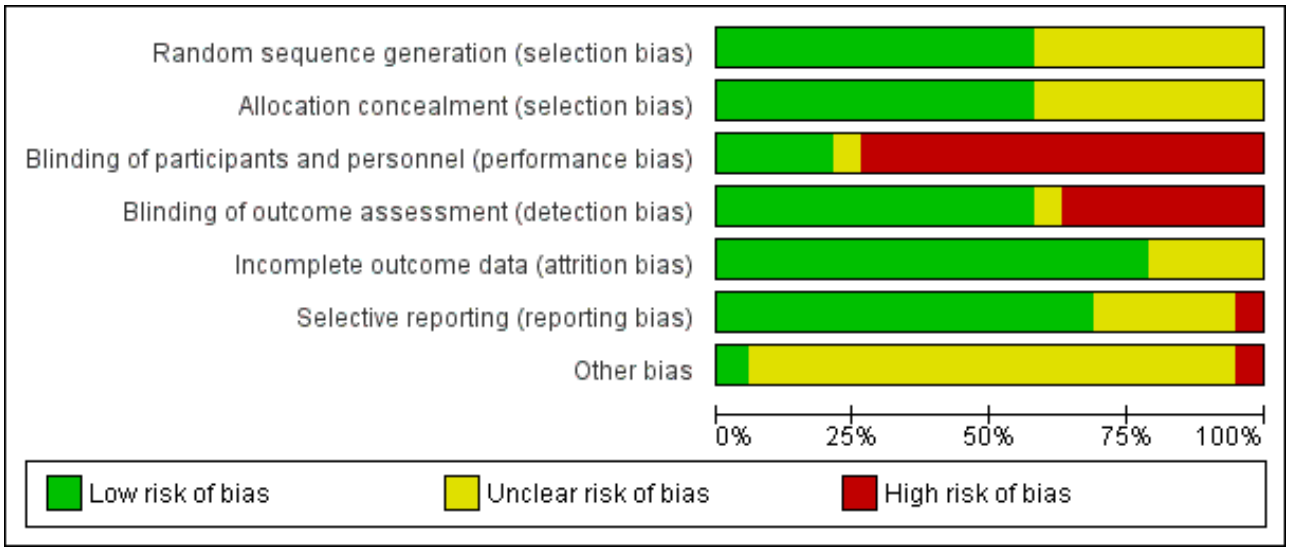


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

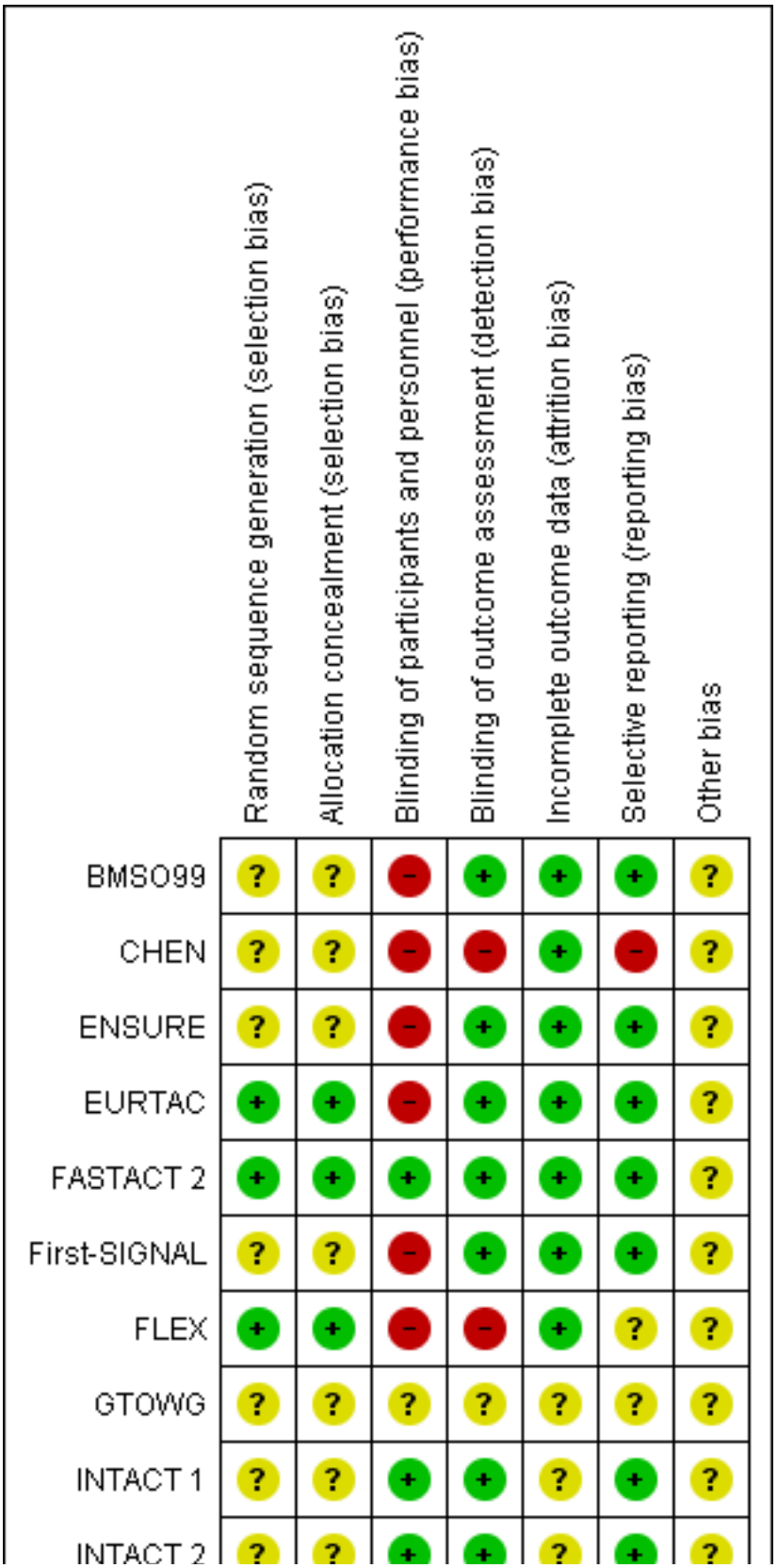
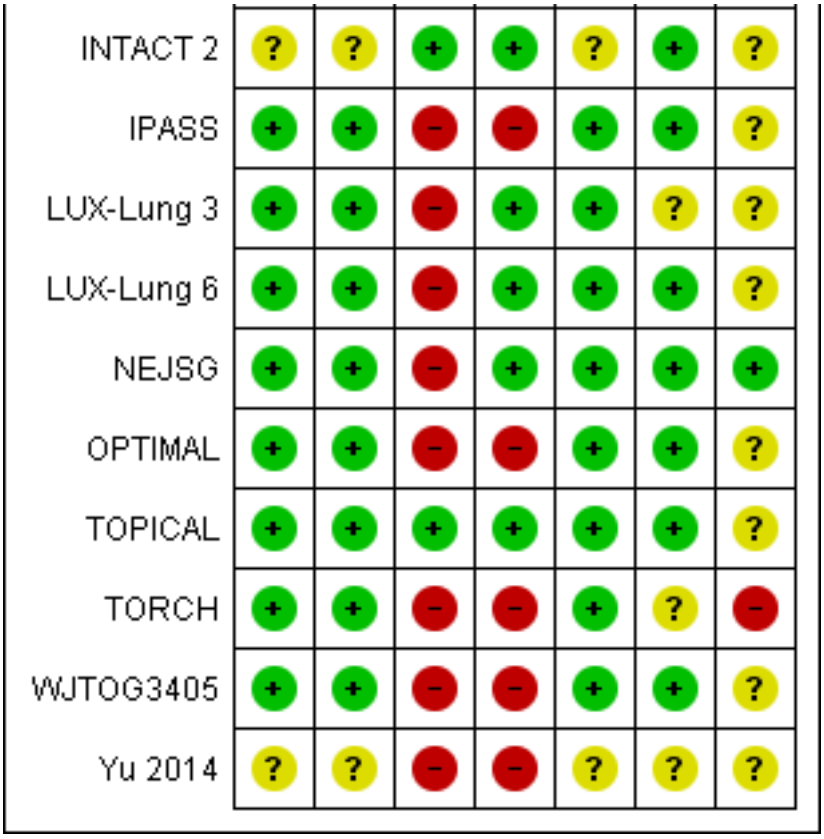


Figure 3. (Continued)



The comparisons with cytotoxic chemotherapy were in general direct, but there was wide variation in the choice of cytotoxic chemotherapy in the comparator arm. This reflects variation in clinical practice, in particular performance status and comorbidity of the NSCLC populations. For example, single-agent vinorelbine, used as the comparator in two of the smaller erlotinib trials (CHEN; GTOWG), is associated with lower toxicity than the more widely given doublet chemotherapy combinations used in the other trials, and participants in both CHEN and GTOWG were selected on the basis of age (older than 70) and not primarily performance status. The trials also varied in the extent to which they included never-smokers or former smokers, and in the male/female ratio. The remaining major factor contributing to heterogeneity was ethnicity, as the eight trials recruiting exclusively in Asia contributed 64% of the participants. All of these factors may contribute to variation in drug handling of both cytotoxic chemotherapy and targeted therapy. Heterogeneity was high for assessment of PFS for erlotinib, gefitinib, and afatinib comparisons in the pooled data.

The results of this review should be interpreted cautiously. Just seven of the included trials recruited only people with EGFR mutations (n = 1672). This means that the data extracted from the remaining 12 trials (n = 645) are derived from subgroups, with all the issues that the interpretation of subgroup data entails. However, it is worth noting that the subgroup of EGFR M+ patients in the IPASS trial, at 261, was larger than the total trial population of four of the EGFR M+ only trials (EURTAC; NEJSG; OPTIMAL; WJTOG3405). It should be further noted that in four trials the tissue analyses were carried out retrospectively on a limited number of samples that were available at the end of the trial (BMSO99; FLEX; INTACT 1; INTACT 2). However, these four trials provided data from only 113 participants, and 80 of these were participants were from the cetuximab trials. We do not believe this factor has an impact on the overall conclusions with respect to the three TKIs.

The confidence limits of the PFS and OS plots were narrow, with the exception of the small trial of erlotinib (CHEN), and suggest the data are precise. We saw wider confidence limits for response, which may reflect the subjective nature of the assessment, even with external review, and current concerns PFS is the better endpoint for trial assessment where cross-over is a factor (Booth 2012).

There is evidence that Asian patients have a different proportion of EGFR M+ and a differing relationship to smoking, which may imply there are differences in the biology of NSCLC between individuals of Asian and non-Asian ethnicity . Of the 2317 participants reported on in this review, 1591 were recruited exclusively in trials conducted in Asian countries. We found no evidence that there is a different set of mutations in Asian and white patients, or differences in their toxicity profiles for the targeted or chemotherapy arms of the included trials.

Potential biases in the review process

We excluded trials that utilised EGFR-targeted treatments but did not report any EGFR mutation testing of participants. However, inspection of review papers and reference lists indicated that in relation to four of these trials (BMSO99; FLEX; INTACT 1; INTACT 2), retrospective analyses of tissue samples from participants had taken place, the results of which were reported in papers separate to the original trial publication. It is possible that there are other

retrospective analyses that we did not identify, however the patient population from any such analyses is likely to be small.

Agreements and disagreements with other studies or reviews

The results are in agreement with the meta-analysis of Ku 2011, which compared gefitinib with first-line chemotherapy. A more recent meta-analysis of 14,570 participants given TKIs in first-line, second-line, and maintenance RCTs also supported gain in PFS in EGFR M+ participants treated with erlotinib and gefitinib (Lee 2013). This analysis included data on subgroups of participants (n = 67) from TALENT, TOPICAL, and TRIBUTE that were not available to us at the time of analysis. The Lee review analysed no data on participant characteristics, toxicity, and quality of life (Lee 2013). Their analysis combined the data from 10 first-line trials in a meta-analysis of OS and PFS, and showed an overall HR of 0.43 (95% CI 0.38 to 0.49; P < 0.001) for PFS and no effect on OS. As described above, we considered this pooling to be inappropriate on statistical grounds, as adjusted and unadjusted data were combined. An updated meta-analysis by the same group focused on seven trials (ENSURE; EURTAC; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405), and concluded that never-smokers, those with tumours with exon 19 deletions, and women had a greater benefit from erlotinib than chemotherapy (Lee 2015). Other reviews have combined data from seven phase III trials, in Hasegawa 2015, and eight phase lll trials, in Haaland 2014, for first-line chemotherapy, and confirmed the benefit in PFS and response. The data on benefit in non-smokers is difficult to interpret in these studies. One network meta-analysis of 12 trials combined first- and second-line treatments, and concluded that erlotinib, gefitinib, and afatinib shared similar efficacy (Liang 2014). Our review of participants across 19 trials includes additional trials and comparable data from the 2317 EGFR M+ participants on afatinib, erlotinib, and gefitinib. A recent individual patient meta-analysis of four RCTs of cetuximab, Pujol 2014, (including BMSO99 and FLEX) in NSCLC reported improved PFS in squamous cell cancers (based on a subgroup analysis) but not in non-squamous carcinomas, although these data were not analysed by mutation status.

The prespecified analysis of the Del19 subgroup across a pooled analysis of both of the afatinib trials demonstrated an OS advantage for afatinib compared to chemotherapy in that subgroup, while the L858R subgroup (codon 21 mutation) showed no OS benefit (Yang 2014). Notably, cross-over to afatinib in the control arm was not allowed, whilst in the majority of comparisons of erlotinib and gefitinib with cytotoxic chemotherapy, cross-over to the corresponding TKI was permitted. Overall, there was a lack of data on OS benefit of EGFR inhibitors, but with a low confidence on this due to the inconsistency and imprecision of the results.

AUTHORS' CONCLUSIONS

Implications for practice

Erlotinib, gefitinib, and afatinib are effective in prolongation of PFS but not OS in EGFR M+ NSCLC patients with acceptable toxicity. Quality of life and response are closely linked, and the available data would favour selection of TKIs over chemotherapy as first-line treatment based on both these criteria, although only six trials reported on quality of life solely in the EGFR M+ population. The majority of trials included people with a performance status (PS) of 1 and 2, but the data on AEs suggest that some PS 3 as well as elderly patients might tolerate the agents better than cytotoxic chemotherapy (CHEN; GTOWG). TKIs may be an alternative to best supportive care in people with EGFR M+ NSCLC unsuitable for chemotherapy. Other reviews have concluded that the cytotoxic chemotherapy standard for non-squamous NSCLC should now be cisplatin and pemetrexed (Brown 2013), at least in patients of good PS. In locations where mutation testing is not available, a decision about the selection of first-line TKI therapy or chemotherapy may have to be made on the basis of histology, gender, smoking history, and ethnicity.

In people with good PS, the intercalated regimen of erlotinib and cytotoxic chemotherapy is another option in view of its preliminary OS benefit in one trial (FASTACT 2). While there was a lack of overall OS benefit, mature data on expected results within two years from the larger trials should provide more definitive guidance.

Our results for AEs underline the evidence for reduced toxicities experienced with TKI therapy versus with cytotoxic chemotherapy. This will have implications for patient care and healthcare costs (Pilkington 2012).

Implications for research

Future trials of these agents should comprise participants with known EGFR mutations, and attempt to clarify the effectiveness in the common mutant subtypes (codons 19, 20, and 21) as well as the small numbers with multiple and rare mutations. There is increasing evidence that people with T790M mutations should be excluded from trials of afatinib, erlotinib, and gefitinib. Irreversible inhibitors of EGFR are under development. Biomarker trials may help to select patients in which optimal activity will be demonstrated; for example codon 19 to 21 mutations are more likely to be associated with receptor internal domain alterations which will not respond to the ligand-binding action of cetuximab (Khambata-Ford 2010), and as the preliminary data presented here have shown, individual TKIs may prove more effective for specific codon alterations. One recent trial still in progress has shown a response rate of 64% in people with tumours harbouring the T790M mutation (Janne 2015). It follows that stratification of NSCLC patients by appropriate molecular profile will evolve progressively with the introduction of new agents.

The role of combination of EGFR-targeted therapy and cytotoxic chemotherapy and the associated toxicity remains to be established, but the data from the BMSO99, FLEX, INTACT 1, and INTACT 2 trials do not favour this approach, either in terms of efficacy or toxicity. The FASTACT 2 trial demonstrated positive outcomes for the combination of erlotinib and cytotoxic chemotherapy given in an intercalated design, however the number of EGFR M+ participants in these trials was small. Cross-over designs with alternative targeted therapies should be initiated by academic groups, as these are unlikely to attract industry funding. Evidence is accumulating of different subgroups of non-squamous NSCLC based on driver gene mutations such as KRAS and the ALK gene rearrangement, and these would appear to be mutually exclusive with the EGFR M+.

Further comparative trials with cytotoxic chemotherapy would seem unlikely to be of value in EGFR M+ patients; the focus should instead be on identifying the predictive value of specific mutations to optimise survival and minimise toxicity from inappropriate therapy (Lee 2015). The majority of studies in this review used a

range of sequencing techniques from a primary tumour biopsy for stratification. Research is currently in progress to assess the utility of less invasive technologies such as cell-free DNA (Murtaza 2013). Future trials should report in detail the degree and duration of symptom control as well as quality of life scores to improve patient selection.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

BMSO99

Methods	Open-label, randomised, multicentre phase III trial conducted in the USA Length of follow-up: not reported The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 17) is retrospective and reported in a paper separate to the primary published paper
Participants	676 people with histologically or cytologically confirmed stage IV, stage IIIB (with malignant pleural effusion), or recurrent (after radiotherapy or surgery) NSCLC with bidimensionally measurable disease Inclusion criteria: > 18 years; ECOG PS < 2. People with previously treated CNS metastases accepted, but people with symptomatic, uncontrolled disease or requiring corticosteroids were not. Prior surgery (4 weeks) or chest radiation (12 weeks) but no prior chemotherapy for NSCLC or EGFR-targeted therapy. Exclusion criteria: previous infusion reactions to chimerised/murine MABs; pregnant/nursing women; history of acute myocardial infarction (3 months prior); grade 2 peripheral neuropathy; inadequate haematologic, hepatic, or renal function. Median age: 64 years Male: 57% Ethnicity: 88% white
Interventions	Treatment arm (8/338 participants EGFR M+): cetuximab plus taxane/carboplatin Comparator arm (9/338 participants EGFR M+): taxane/carboplatin

BMSO99 *(Continued)*

	Cetuximab, the first dose was 400 mg/m^2, 120-minute IV, with subsequent doses of 250 mg/m^2, 60-minute IV, weekly until disease progression or intolerable toxicity, even after completion of chemotherapy. Paclitaxel 225 mg/m^2, 3-hour IV, or docetaxel 75 mg/m^2, 1-hour IV with carboplatin (AUC = 6, 30-minute IV) on day 1 every 3 weeks until disease progression or intolerable toxicity for 6 cycles
Outcomes	Primary outcome: PFS (based on modified WHO criteria) Secondary outcomes: ORR, OS, QoL, safety
Mutation Assessment Method	QIAamp
Exons assessed	18 to 21
Notes	The trial was originally designed as a randomised phase II trial to provide non-comparative data on the efficacy of cetuximab combined with standard chemotherapy (ORR as primary endpoint). 10 months after accrual initiation, the protocol was amended to be conducted as a phase III trial to evaluate the addition of cetuximab to taxane plus carboplatin, with a primary endpoint of PFS. Participant accrual was increased from 300 to 660

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on randomisation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent radiological assessment was undertaken
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants in cetuximab arm did not receive treatment; 18 participants in the taxane-only arm did not receive treatment. Reasons not given. However, ITT analysis was carried out
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Unclear risk	Trial support from drug manufacturers

CHEN

Methods	Open-label, randomised phase II trial conducted in Taiwan Length of follow-up: not reported

CHEN *(Continued)*

	The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 24) is presented as subgroup analysis in the primary published paper
Participants	113 participants aged 70 years or older with histologic or cytologic diagnosis of inoperable NSCLC who had never received chemotherapy, targeted therapy, or hormonal therapy were entered into the trial after giving informed consent. Inclusion criteria: ECOG PS of 0 to 3; measurable lesion(s); no previous radiotherapy on measurable lesion(s); adequate bone marrow reserve with a granulocyte count more than or equal to 1500/mm^3, platelets more than or equal to 100,000/mm^3, and haemoglobin more than or equal to 10 g/dL. Exclusion criteria: Previous therapy, symptomatic or unstable brain metastases, inadequate liver or renal function, or uncontrolled systemic disease. Median age: 77 years Male: 81% Ethnicity: 100% East Asian
Interventions	Treatment arm (9/57 participants EGFR M+): erlotinib 150 mg/daily Comparator arm (15/56 participants EGFR M+): vinorelbine 60 mg/m^2 days 1 and 8 of every 3-weekly cycle Responding participants and those with stable disease continued treatment until disease progression or completion of 6 cycles. Participants could continue treatment beyond 6 cycles provided their disease was controlled
Outcomes	Primary outcome: ORR Secondary outcomes: OS, PFS (RECIST version 1 criteria), disease control rate, tolerability, QoL (FACT-L)
Mutation Assessment Method	VarientSEQr
Exons assessed	18 to 21
Notes	All participants were aged 70 years or older. Vinorelbine dose increased to 80 mg/m^2 beginning from cycle 2 if no toxicity of grade 2 or higher

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states that participants were randomised with stratification. No other information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of independent assessment of PFS

CHEN *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for
Selective reporting (reporting bias)	High risk	The protocol states that time to progression is a secondary outcome. This is not mentioned or reported in the published paper
Other bias	Unclear risk	Trial partially sponsored by pharmaceutical company

ENSURE

Methods	Open-label phase III RCT conducted in Asia Length of follow-up: 28.9 (erlotinib), 27.1 (cytotoxic chemotherapy)
Participants	217 people with stage IIIB/IV non-small cell lung cancer with EGFR mutations in their tumours
Interventions	Erlotinib (n = 110) 150 mg once daily until progression/unacceptable toxicity Gemcitabine plus cisplatin (n = 117) gemcitabine 1250 mg/m^2 IV days 1 and 8 plus cisplatin 75 mg/m^2 IV day 1, every 3 weeks, for up to 4 cycles.
Outcomes	Primary PFS (RECIST) Secondary ORR, DCR, OS, AEs, QoL
Mutation Assessment Method	cobas EGFR Mutation Test (Roche Molecular Systems)
Exons assessed	19, 21
Notes	Estimated primary completion date: December 2015. ClinicalTrials.gov identifier: NCT01342965 Trial ended early after interim analysis (73% of PFS events). PFS data cutoff July 2012 and OS data cutoff April 2014

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description given
Allocation concealment (selection bias)	Unclear risk	No description given
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label
Blinding of outcome assessment (detection bias)	Low risk	Independent radiological assessment used as a sensitivity analysis

ENSURE *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in the analyses
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported
Other bias	Unclear risk	Trial stopped after interim analysis. Trial sponsored by pharmaceutical company

EURTAC

Methods	Open-label, randomised phase III trial conducted in Spain, France, and Italy Length of follow-up (months): 41 (erlotinib) and 35 (cytotoxic chemotherapy)
Participants	173 people with NSCLC and EGFR mutations. Inclusion criteria: Histological diagnosis of stage IIIB (with pleural effusion) or stage IV NSCLC (based on the 6th TNM staging system), measurable or evaluable disease. Activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21), age older than 18 years, and no history of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended ≥ 6 months before entry to trial). Exclusion criteria: Non-EGFR mutated patients, previous chemotherapy for metastatic disease. Median age: 65 years Male: 28% Ethnicity: 92% white
Interventions	Treatment arm (86/86 participants EGFR M+): erlotinib 150 mg/daily until disease progression, toxicity, or withdrawal of consent Comparator arm (87/87 participants EGFR M+): cisplatin 75 mg/m^2 on day 1, docetaxel 75 mg/m^2 on day 1, or gemcitabine 1250 mg/m^2 on day 1 and 8. Cycle of 3 weeks for up to 4 cycles People who were ineligible for cisplatin treatment received IV carboplatin chemotherapy instead (3-week cycles of AUC 6 on day 1 with 75 mg/m^2 docetaxel on day 1, or AUC 5 on day 1 with 1000 mg/m^2 gemcitabine on days 1 and 8)
Outcomes	Primary outcome: PFS (RECIST version 1 criteria) Secondary outcomes: OS, ORR
Mutation Assessment Method	ABI Prism 3130 Genetic Analyzer
Exons assessed	19, 21
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled participants were EGFR positive. Trial enrolment was stopped at interim data analysis as trial had met primary endpoint

Risk of bias

EURTAC *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation, stratified by EGFR mutation type and ECOG performance status
Allocation concealment (selection bias)	Low risk	Centralised allocation system used
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS and treatment responses were confirmed by an external review of CT scans by a central review board
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported (trial protocol available via NICE STA process)
Other bias	Unclear risk	Trial sponsored in part by pharmaceutical company. Trial enrolment was stopped at interim data analysis as trial had met primary endpoint

FASTACT 2

Methods	Double-blind, placebo-controlled, randomised phase III trial conducted in Asia Length of follow-up (months): erlotinib = 28; cytotoxic chemotherapy = 28 The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 97) is presented as a subgroup analysis in the primary published paper
Participants	451 people with stage IIIB/IV NSCLC Inclusion criteria: ECOG PS 0 or 1; measurable disease according to RECIST version 3.0. Exclusion criteria: Previous treatment with agents targeting the HER axis; previous systemic antitumour treatment; adjuvant or neoadjuvant treatment for non-metastatic disease within 6 months; surgery less than 4 weeks before the trial; localised radiotherapy; brain metastasis; any unstable illness; people known to be HIV positive. Median age: 58 years Male: 60% Ethnicity: 100% Southeast Asian
Interventions	Treatment arm (49/226 participants EGFR M+): erlotinib 150 mg per day plus gemcitabine (1250 mg/m^2 on days 1 and 8 of a 4-week cycle, intravenously) plus platinum (carboplatin 5 × AUC or cisplatin 75 mg/m^2 on day 1 of a 4-week cycle) Comparator arm (48/225 participants EGFR M+): placebo plus gemcitabine (1250 mg/m^2 on days 1 and 8 of a 4-week cycle, intravenously) plus platinum (carboplatin 5 × AUC or cisplatin 75 mg/m^2 on day 1 of a 4-week cycle) plus placebo

FASTACT 2 *(Continued)*

Outcomes	Primary outcome: PFS Secondary outcomes: OS, ORR, duration of response, TTP, safety
Mutation Assessment Method	cobas 4800 system
Exons assessed	19, G719X, L858R, or L861Q
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in a 1:1 ratio by use of a central randomisation programme with a minimisation algorithm
Allocation concealment (selection bias)	Low risk	Central randomisation and drug-pack allocation were assigned by use of an interactive internet response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Everyone outside the company responsible for the interactive internet response system was masked to treatment allocation with the exception of a small independent group that was responsible for monitoring data and safety early in the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent review committee masked to treatment assignment reviewed all tumour images and determined tumour response and progression status
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in final analysis. ITT analysis conducted. Equal numbers (n = 4) in each arm did not receive allocated treatment
Selective reporting (reporting bias)	Low risk	All outcomes reported in protocol were assessed and presented in published paper
Other bias	Unclear risk	Trial sponsored in part by pharmaceutical company

First-SIGNAL

Methods	Open-label, randomised, multicentre phase III trial conducted in Korea Length of follow-up (months): 35 The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 42) is presented as a subgroup analysis in the primary published paper
Participants	313 Korean never-smoker patients with stage IIIB or IV lung adenocarcinoma Inclusion criteria: Chemotherapy-naive never-smokers older than 18 years with stage IIIB (ineligible for curative radiotherapy) or IV adenocarcinoma of the lung with measurable or nonmeasurable disease, PS of 0 to 2, and adequate bone marrow, liver, and renal function. Exclusion criteria: Severe hypersensitivity to gefitinib or any constituents of this product; any evidence of clinically active interstitial lung disease; severe or uncontrolled systemic disease; concomitant use of phenytoin, carbamazepine, rifampin, barbiturate, or St John's wort; and non-stable brain metastasis.

First-SIGNAL *(Continued)*

	Median age: 57 years Male: 11% Ethnicity: 100% East Asian
Interventions	Treatment arm (26/159 participants): gefitinib 250 mg/daily until disease progression Comparator arm (16/154 participants): cisplatin 75 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8. Cycle of 3 weeks for up to 9 cycles
Outcomes	Primary outcome: OS Secondary outcomes: PFS (WHO criteria), QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the lung cancer–specific module LC13), ORR
Mutation Assessment Method	QIAamp
Exons assessed	19 to 21
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were recruited to the trial by 1:1 random assignment and stratified by sex, PS, and disease stage. No details of randomisation procedures reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial is open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent blinded assessment of PFS is reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for (4 withdrew consent in gemcitabine arm prior to treatment)
Selective reporting (reporting bias)	Low risk	No protocol available, but all outcomes stated in paper as measured are reported
Other bias	Unclear risk	Trial sponsored in part by a pharmaceutical company

FLEX

Methods	Open-label, randomised phase III trial conducted internationally Length of follow-up (months): cetuximab = 24; cytotoxic chemotherapy = 24

FLEX *(Continued)*

	The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 64) is retrospective and reported in a paper published separately from the main analyses
Participants	1125 chemotherapy-naive patients with histologically or cytologically proven stage IIIB or IV NSCLC and IHC evidence of EGFR expression in at least 1 positively stained tumour cell Inclusion criteria: > 18 years, ECOG PS 0 to 2, adequate organ function, at least 1 bidemensionally measurable tumour lesion. Exclusion criteria: Brain metastases, previous treatment with EGFR-targeted drugs or MABs, major surgery within previous 4 weeks, chest irradiation 12 weeks prior to trial entry, active infection, pregnancy, symptomatic peripheral neuropathy Median age: 59 years Male: 70% Ethnicity: 85% white
Interventions	Treatment arm (28/557 participants EGFR M+): cetuximab plus cisplatin and vinorelbine. Cetuximab starting dose of 400 mg/m^2 intravenous infusion over 2 hrs on day 1, and from day 8 onwards at 250 mg/m^2 over 1 hr per week. Cisplatin 80 mg/m^2 intravenous infusion on day 1, and vinorelbine 25 mg/m^2 intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles. Comparator arm (36/568 participants EGFR M+): cisplatin plus vinorelbine. Cetuximab was continued after the end of chemotherapy until disease progression or unacceptable toxicity occurred
Outcomes	Primary outcome: OS Secondary outcomes: PFS (modified WHO criteria), TTP, ORR, QoL, AEs
Mutation Assessment Method	DxS EGFR 29 Mutation Test Kit
Exons assessed	19
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Centralised IVRS used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label. No evidence of independent assessment of radiological outcomes

FLEX *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for. ITT analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes reported except disease control rate
Other bias	Unclear risk	Trial supported by pharmaceutical company

GTOWG

Methods	A randomised phase II trial conducted in Germany Length of follow-up (months): not reported The trial included a mixed patient population. The analysis of data for participants with EGFR M+ tumours (n = 10) is retrospective in the primary publication
Participants	284 people aged 70 years or older with stage IIIB or IV NSCLC
Interventions	Treatment arm (144 participants): erlotinib 150 mg/daily Comparator arm (140 participants): carboplatin AUC 5 d 1 and vinorelbine 25 mg/m^2 day 1, 8 every 21 days for up to 6 cycles
Outcomes	Primary outcome: PFS (RECIST criteria) Secondary outcomes: OS, response, tolerability, QoL
Mutation Assessment Method	Direct
Exons assessed	Not reported
Notes	The patient population was over 70 years old. Only exons 17 and 19 were screened using the ABI 3500 Genetic Analyzer. Quality of life is not reported, nor is OS or PFS for EGFR M+ participants. Trial information taken from poster provided by trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised. No information provided. Trial information taken from conference abstract
Allocation concealment (selection bias)	Unclear risk	No information. Trial information taken from conference abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided. Trial information taken from conference abstract
Blinding of outcome assessment (detection bias)	Unclear risk	No information

GTOWG *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants did not receive treatment, but reasons not reported
Selective reporting (reporting bias)	Unclear risk	Quality of life not reported
Other bias	Unclear risk	Pharmaceutical company support unclear

INTACT 1

Methods	Double-blind, randomised, placebo-controlled phase III trial conducted internationally Length of follow-up (months): 15.9 Combined retrospective molecular analysis of INTACT 1 and 2 participants (combined total of 32) is reported in a publication separate to the main trial publication
Participants	1093 people histologically/cytologically confirmed NSCLC, locally advanced stage III disease not curable with surgery or radiotherapy or stage IV disease Inclusion criteria: Aged 18 years or older and WHO PS of 0 to 2. Exclusion criteria (main): Previous chemotherapy (prior surgery or localised radiation were allowed); hypersensitivity to mannitol, corticosteroids, H2-antagonists, antihistamines, or agents formulated with polyoxyethylated castor oil; radiotherapy within the last 2 weeks; unresolved toxicity from previous radiation therapy or incomplete healing from previous surgery; pre-existing motor or sensory neurotoxicity; severe or uncontrolled systemic disease; recent conditions requiring medication or uncontrolled significant active infections; pregnant or breastfeeding; coexisting malignancies or malignancies diagnosed within the last 5 years with the exception of basal-cell carcinoma or cervical cancer in situ; mixed NSCLC plus small-cell lung cancer. Median age: 60 years Male: 74% Ethnicity: 90% white
Interventions	Treatment arm A (365 participants): gefitinib 500 mg/daily plus gemcitabine 1250 mg/m^2 IV 30 minutes on days 1 and 8 and cisplatin 80 mg/m^2 after gemcitabine administration on day 1 only Treatment arm B (365 participants): gefitinib 250 mg/daily plus gemcitabine and cisplatin Comparator arm (363 participants): placebo plus gemcitabine and cisplatin Chemotherapy was administered in 3-week cycles for a total of 6 cycles; subsequently, participants continued on gefitinib or placebo until disease progression
Outcomes	Primary outcome: OS Secondary outcomes: TTP (RECIST), response rate, and safety
Mutation Assessment Method	BigDye Terminator
Exons assessed	18 to 21

INTACT 1 *(Continued)*

Notes	Number of EGFR M+ participants unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned. No information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No independent review, but outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	No protocol available, but all outcomes stated in paper as measured are reported
Other bias	Unclear risk	Supported by a grant from AstraZeneca, Wilmington, DE

INTACT 2

Methods	Double-blind, randomised, placebo-controlled phase III trial conducted mainly in the USA Length of follow-up (months): not reported Combined retrospective molecular analysis of INTACT 1 and 2 participants (combined total of 32) is reported in a publication separate to the main trial publication
Participants	1037 people with histologically confirmed NSCLC, unresectable stage III or IV disease Inclusion criteria: No prior chemotherapy, aged 18 years or older, and WHO PS 0 to 2. Exclusion criteria (main): Mixed NSCLC or small-cell lung cancer, brain metastases that were newly diagnosed or had not been treated with surgery or radiation, previously treated CNS metastases or spinal-cord compression in the absence of clinically stable disease, less than 2 weeks since radiotherapy, unresolved toxicity from prior radiotherapy or incomplete healing from surgery, severe systemic disease, pregnancy or breastfeeding, and hypersensitivity to mannitol, corticosteroids, H2-antagonists, antihistamines, or agents formulated with polyoxyethylated castor oil. Median age: 62 years Male: 59% Ethnicity: 90% white

INTACT 2 *(Continued)*

Interventions	Treatment arm A (347 participants): gefitinib 500 mg/daily plus intravenous paclitaxel 225 mg/m^2 over 3 hours on day 1 of a 3-week cycle immediately followed by intravenous carboplatin area under concentration/time curve of 6 mg/min/mL over 15 to 30 minutes on day 1 Treatment arm B (345 participants): gefitinib 250 mg/daily plus intravenous paclitaxel 225 mg/m^2 over 3 hours on day 1 of a 3-week cycle immediately followed by intravenous carboplatin area under concentration/time curve of 6 mg/min/mL over 15 to 30 minutes on day 1 Comparator arm (345 participants): placebo plus intravenous paclitaxel 225 mg/m^2 over 3 hours on day 1 of a 3-week cycle immediately followed by intravenous carboplatin area under concentration/time curve of 6 mg/min/mL over 15 to 30 minutes on day 1 Chemotherapy was continued for 6 cycles in the absence of disease progression. Thereafter, participants were maintained on gefitinib or placebo (control arm) until disease progression or drug intolerance
Outcomes	Primary outcome: OS Secondary outcomes: TTP (RECIST criteria), ORR, symptom control, QoL, AEs
Mutation Assessment Method	BigDye Terminator
Exons assessed	18 to 21
Notes	Number of EGFR M+ participants unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No independent review, but outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	No protocol available, but all outcomes stated in paper as measured are reported
Other bias	Unclear risk	Supported by a grant from AstraZeneca, Wilmington, DE

IPASS

Methods	Open-label, randomised phase III trial conducted in East Asia Length of follow-up (months): 1 The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 261) is retrospective and reported in a paper published separately from the main analyses
Participants	1217 people who had advanced pulmonary adenocarcinoma and who were non-smokers or former light smokers Inclusion criteria: 18 years of age or older, histologically or cytologically confirmed stage IIIB or IV NSCLC with histologic features of adenocarcinoma (including bronchoalveolar carcinoma), were non-smokers (people who had smoked < 100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤ 10 pack-years of smoking), and who had had no previous chemotherapy or biologic or immunologic therapy. Median age: 57 years Male: 20% Ethnicity: 99% East Asian
Interventions	Treatment arm (132/609 participants EGFR M+): gefitinib 250 mg/daily Comparator arm (129/608 participants EGFR M+): carboplatin at a dose calculated to produce an area under the concentration–time curve of 5.0 or 6.0 mg per milliliter per minute, administered intravenously over a period of 15 to 60 minutes in cycles of once every 3 weeks for up to 6 cycles and paclitaxel (200 mg/m^2), administered intravenously over a 3-hour period on the first day of the cycle in cycles of once every 3 weeks for up to 6 cycles
Outcomes	Primary outcome: PFS (RECIST criteria) Secondary outcomes: OS, ORR, QoL (FACT–L questionnaire, Trial Outcome Index, and reduction in symptoms, assessed with LCSS score), safety, and adverse-event profile
Mutation Assessment Method	DxS EGFR 29 Mutation Test Kit
Exons assessed	18 to 21
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of dynamic balancing randomisation procedure. Assume computer program used
Allocation concealment (selection bias)	Low risk	Although not reported in paper, interactive voice response system was used (source AstraZeneca evidence submission to NICE)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	PFS was assessed according to RECIST criteria. However, no independent verification of assessments was reported

IPASS *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	No selective reporting occurred
Other bias	Unclear risk	Trial sponsored by pharmaceutical company

LUX-Lung 3

Methods	Open-label, international phase III trial Length of follow-up (months): 16.4
Participants	345 participants with adenocarcinoma, stage IIIB or IV, EGFR M+, and ECOG PS of 0 to 1 Inclusion criteria: Activating mutation in EGFR treatment-naive advanced lung adenocarcinoma; good performance status (ECOG 0 or 1); adequate end-organ function; and measurable disease using RECIST version 1.1. Median age: 61 years Male: 34.5% Ethnicity: 71% East Asian
Interventions	Treatment arm (345/345 participants EGFR M+): afatinib 40 mg/day, escalated to 50 mg if limited adverse events observed in cycle 1 until progression Comparator arm (115/115 participants EGFR M+): cisplatin 75 mg/m^2 and pemetrexed every 21 days for up to 6 cycles
Outcomes	Primary outcome: PFS Secondary outcomes: OS, ORR, DCR, tumour shrinkage, QoL (EORTC QLQ-C30 and QLQ-LC13), AEs
Mutation Assessment Method	therascreen EGFR 29
Exons assessed	18 to 21
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Company's standard validated random number-generating system was used to generate the randomisation schedules, verified by a trial-independent statistician
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally using IVRS/IWRS

LUX-Lung 3 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label trial but with independent review
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Outcomes measured unclear from slides
Other bias	Unclear risk	Trial sponsored in part by pharmaceutical company

LUX-Lung 6

Methods	Open-label, randomised phase III trial Length of follow-up (months): 16.6
Participants	364 Asian patients all with therascreen positive EGFR M+ NSCLC Inclusion criteria: Pathologically confirmed and previously untreated stage IIIB or IV lung adenocarcinoma ECOG PS 0 or 1; measurable disease according to RECIST version 1.1; adequate organ function. Tumour tissue had to be EGFR M+ at the screening stage. Median age: 58 years Male: 34% Ethnicity: 90% Chinese
Interventions	Treatment arm (242/242 participants EGFR M+) afatinib 40 mg/day Comparator arm (122/122 participants EGFR M+) gemcitabine 1000 mg/m^2 d 1 and 8 and cisplatin 75 mg/m^2 for up to 6 cycles
Outcomes	Primary outcome: PFS by central independent review Secondary outcomes: overall response rate, disease control rate, OS, safety, QoL
Mutation Assessment Method	therascreen EGFR 29
Exons assessed	19 to 21
Notes	HR 0.26 P < 0.0001 in favour of afatinib. Participant-reported outcomes pain, cough, and dyspnoea all significantly improved

Risk of bias

Bias	Authors' judgement	Support for judgement

LUX-Lung 6 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was done centrally with a random number-generating system and an interactive internet and voice response system
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial. Clinicians and participants were not masked to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial investigators who performed assessments of participant-reported outcomes and safety, along with supportive assessments of tumour response (used for sensitivity analyses), were not masked to treatment assignment, but the independent central imaging review group were
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for. ITT analysis conducted
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Trial sponsored in part by pharmaceutical company

NEJSG

Methods	Open-label, randomised phase III trial conducted in Asia Length of follow-up (months): 24
Participants	230 people with metastatic NSCLC and EGFR mutations Inclusion criteria: NSCLC with EGFR mutations, chemonaive, aged < 75 years Exclusion criteria: Previous chemotherapy/targeted therapy, presence of resistant EGFR mutation T790M Mean age: 62 years Male: 36% Ethnicity: 100% Chinese
Interventions	Treatment arm (114/114 participants EGFR M+): gefitinib 250 mg/daily until disease progression, toxicity, or withdrawal of consent Comparator arm (114/114 participants EGFR M+): carboplatin, dose equivalent to an area under the concentration–time curve of 6, given intravenously over a 1-hour period on day 1 every 3 weeks and paclitaxel 200 mg/m^2, given intravenously over a 3-hour period every 3 weeks. Treatment was given for at least 3 cycles until unacceptable toxicity or withdrawal of consent
Outcomes	Primary outcome: PFS (RECIST version 1 criteria) Secondary outcomes: OS, ORR, time to the deterioration of performance status, AEs

NEJSG *(Continued)*

Mutation Assessment Method	PNA-LNA
Exons assessed	19 to 21 (excluding T90M)
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled participants were EGFR positive

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with block size of 2. Stratification factors of mutation type, histology, and smoking status (source: company submission to NICE erlotinib 1st line). Assume computer program used
Allocation concealment (selection bias)	Low risk	Centralised allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent radiological review conducted
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	None identified

OPTIMAL

Methods	Open-label, randomised, multicentre phase III trial conducted in China Length of follow-up (months): not reported
Participants	165 people with NSCLC Inclusion criteria: Confirmed EGFR mutations in exon 19 or 21; more than 18 years of age; histologically confirmed advanced or recurrent stage IIIB or IV NSCLC measurable disease ECOG PS 0–2; adequate haematological, biochemical, and organ function Exclusion criteria: Uncontrolled brain metastases or had received previous systemic anticancer therapy for advanced disease Median age: 58 years Male: 40.5% Ethnicity: 100% Chinese

OPTIMAL *(Continued)*

Interventions	Treatment arm (83/83 participants EGFR M+): erlotinib 150 mg/daily until disease progression Comparator arm (82/82 participants EGFR M+): carboplatin (area under the curve = 5) on day 1 of a 3-week cycle and gemcitabine 1000 mg/m^2 on days 1 and 8 for up to 4 cycles
Outcomes	Primary outcome: PFS (RECIST version 1 criteria) Secondary outcomes: OS, ORR, TTP, duration of response, safety, QoL (FACT-L questionnaire and Lung Cancer Subscale)
Mutation Assessment Method	Direct
Exons assessed	19 to 21
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled participants were EGFR M+

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned (1:1) to either erlotinib or chemotherapy by dynamic minimisation procedure with Mini randomisation software. Central randomisation was done by a clinical research organisation
Allocation concealment (selection bias)	Low risk	Centralised allocation by e-mail and telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No independent review of radiological outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Trial sponsored by pharmaceutical company

TOPICAL

Methods	Double-blind, placebo-controlled, randomised, multicentre phase III trial conducted in the UK Length of follow-up (months): not reported The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 28) is reported in the main paper

TOPICAL *(Continued)*

Participants	670 people with newly diagnosed, pathologically confirmed NSCLC; stage IIIB or IV disease; chemotherapy naive; no symptomatic brain metastases; deemed unsuitable for chemotherapy because of poor ECOG PS (PS ≥ 2) or presence of several comorbidities. Inclusion criteria: Newly diagnosed, pathologically confirmed NSCLC; stage IIIB or IV disease; chemotherapy naive; no symptomatic brain metastases; deemed unsuitable for chemotherapy because of poor ECOG PS (≥ 2) or presence of several comorbidities (including impaired renal function with creatinine clearance < 60 mL/min), or both; estimated life expectancy of at least 8 weeks; older than 18 years; Exclusion criteria: Previous treatment with any biological anticancer therapy; previous palliative radiotherapy (except to bone metastases, within the previous 2 weeks); pregnant or lactating women; evidence of significant laboratory finding or concurrent uncontrolled medical illness judged to potentially interfere with the trial treatment; present treatment with a COX-2 inhibitor. Median age: 77 years Male: 61% Ethnicity: 97% white
Interventions	Treatment arm (17/350 participants EGFR M+): erlotinib 150 mg/daily Comparator arm (11/320 participants EGFR M+): placebo
Outcomes	Primary: OS Secondary: PFS, QoL, AEs
Mutation Assessment Method	Sequenom OncoCarta Panel v1.0
Exons assessed	19, 21
Notes	The trial set out to assess the benefits of erlotinib in a population of patients with NSCLC who were considered unsuitable for chemotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised with a computer-generated sequence with a block size of 10
Allocation concealment (selection bias)	Low risk	Randomisation was done by site staff telephoning the Cancer Research UK and University College London Cancer Trials Centre. All investigators, clinicians, and participants were masked to assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, clinicians, and participants were masked to assignment. Use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators, clinicians, and participants were masked to assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for. ITT analysis conducted

TOPICAL *(Continued)*

Selective reporting (reporting bias)	Low risk	All specified outcomes reported
Other bias	Unclear risk	Risk of participants in erlotinib arm developing rash, thereby disclosing treatment allocation. Partial funding from pharmaceutical company

TORCH

Methods	Open-label, randomised phase III trial conducted in Italy and Canada Length of follow-up (months): 24.3 The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 39) is presented as subgroup analysis in the primary publication
Participants	760 people with NSCLC Inclusion criteria: Histologically or cytologically confirmed NSCLC stage IIIB (with malignant pleural effusion or supraclavicular nodes) or IV, at least 1 target or non-target lesion, age younger than 70 years (no age limits for Canadian centres), ECOG PS 0 to 1. People at first diagnosis and those with recurrence after surgery were eligible. Exclusion criteria: Prior treatment with anti-EGFR agents; history of prior invasive malignancy or inadequate bone marrow; any unstable systemic disease, including active infections and significant cardiovascular, hepatic, renal, or metabolic disease; inflammatory eye surface changes; inability to take or absorb oral medications. Median age: 62.5 years Male: 66% Ethnicity: 96% white
Interventions	Treatment arm (19/380 participants EGFR M+): erlotinib 150 mg/daily until disease progression Comparator arm (20/380 participants EGFR M+): cisplatin 80 mg/m^2 intravenously on day 1 and gemcitabine 1200 mg/m^2 intravenously per day on days 1 and 8 every 3 weeks until progression
Outcomes	Primary outcome: OS Secondary outcomes: Total PFS, time from random assignment to progression after second-line treatment or death if it occurred before second progression, or last follow-up visit for participants not included in the previous 2 categories PFS after first-line therapy (first PFS), defined as the time from random assignment to progression after first-line treatment, or death if it occurred before first progression, or last follow-up visit for participants not included in the previous 2 categories ORR, defined as the number of participants with complete or partial response at any time divided by the total number of participants enrolled onto each arm (All based on RECIST criteria.) Toxicity
Mutation Assessment Method	Direct

TORCH *(Continued)*

Exons assessed	19
Notes	The trial was terminated early because non-inferiority of the experimental arm was demonstrated. This was a 2-stage trial with erlotinib given as first-line treatment and cisplatin plus gemcitabine as second-line treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were centrally randomly assigned to the 2 treatment arms (1:1 ratio) through a centralised automated minimisation procedure by using histology (adenocarcinoma vs other), smoking status (never- vs ever-smoker), sex, age (<70 vs≥70years), centre, and PS (0 vs 1) as strata
Allocation concealment (selection bias)	Low risk	Centralised admin system used
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of independent assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Paper states that further secondary endpoints, including quality of life, comparisons of resource use, and studies of exploratory biomarkers in tumour and blood samples, are not reported in this article
Other bias	High risk	The trial was stopped early because non-inferiority of the experimental arm was demonstrated. The trial was funded by a pharmaceutical company

WJTOG3405

Methods	Open-label, randomised, multicentre phase III trial conducted in Japan Length of follow-up: 59.1 months
Participants	177 chemotherapy-naive patients aged 75 years or younger and diagnosed with stage IIIB/IV NSCLC or postoperative recurrence harbouring EGFR mutations. (5 people were excluded after randomisation.) Inclusion criteria: Histologically or cytologically confirmed NSCLC, harbouring activating EGFR mutations (either exon 19 deletion or L858R in exon 21), aged 75 years or younger, WHO PS 0 to 1, measurable or non-measurable disease, and adequate organ function. Exclusion criteria: Previous drug therapy targeting 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.

WJTOG3405 *(Continued)*

	Median age: 64 years Male: 36% Ethnicity: 100% Japanese
Interventions	Treatment arm (86/86 participants EGFR M+): gefitinib 250 mg/daily Comparator arm (86/86 participants EGFR M+): cisplatin 80 mg/m^2, IV over 90 min once every 3-week cycle and docetaxel 60 mg/m^2, administered IV over 1 hr once every 3-week cycle Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the participant to discontinue treatment, serious non-compliance with the protocol, or completion of 3 to 6 chemotherapy cycles. Further therapy after progression of the disease was at the physician's discretion
Outcomes	Primary outcome: PFS (RECIST criteria) Secondary outcomes: OS, ORR, disease control rate, safety
Mutation Assessment Method	PNA-LNA
Exons assessed	19, 21
Notes	All participants were EGFR M+

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to each treatment group at the data centre using a desktop computer programmed for the minimisation method
Allocation concealment (selection bias)	Low risk	Centralised allocation (see above)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No independent verification of PFS
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	No concern over selective reporting
Other bias	Unclear risk	7 authors had received remuneration from pharmaceutical companies, including AstraZeneca. The trial group is non-profit-making, but receives unrestricted funding from several pharmaceutical companies

Yu 2014

Methods	Open-label, single-centre phase II trial Length of follow-up (months): 35 The trial included a mixed patient population. The analysis of EGFR M+ data only (n = 31) is presented as subgroup analysis in the primary publication
Participants	117 chemonaive patients with advanced (stage IIIB or IV) non-squamous NSCLC. ECOG 0 or 1. Mean age: 55 years Male: 50% Ethnicity: 100% Chinese
Interventions	Treatment arm (13/58 participants EGFR M+): gefitinib 250 mg days 3 to 16 + pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 or carboplatin AUC = 5 every 3 weeks up to 6 cycles Comparator arm (18/59 participants EGFR M+): pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 or carboplatin AUC = 5 every 3 weeks up to 6 cycles
Outcomes	Primary outcome: non-progression rate (RECIST 1.0) Secondary outcomes: ORR, PFS, OS, AE
Mutation Assessment Method	Direct sequencing
Exons assessed	18 to 21
Notes	Treatment in both arms was administered for a maximum of 6 cycles

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of independent radiological assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Protocol not available, but all stated outcomes are reported on
Other bias	Unclear risk	No other bias identified

AE: adverse event
AFA: afatinib
AUC: area under the curve
CET: cetuximab
CNS: central nervous system
CT: computed tomography
DCR: disease control rate
ECOG PS: Eastern Cooperative Oncology Group Performance Status
EGFR M+: epidermal growth factor receptor mutation positive
EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - lung cancer-specific module
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
ERL: erlotinib
FACT-L: Functional Assessment of Cancer Therapy - Lung
GEF: gefitinib
HER: human epidermal growth factor receptor
HIV: human immunodeficiency virus
HR: hazard ratio
IHC: immunohistochemistry
ITT: intention to treat
IV: intravenous
IVRS: interactive voice response system
IWRS: interactive web response system
LCSSS: Lung Cancer Symptom Scale
MAB: monoclonal antibody
NICE: National Institute for Health and Care Excellence
NSCLC: non-small cell lung cancer
ORR: overall response rate
OS: overall survival
PFS: progression-free survival
PS: performance status
QoL: quality of life
RCT: randomised controlled trial
RECIST: Response Evaluation Criteria in Solid Tumors
STA: single technology appraisal
TNM: tumor-node-metastasis
TTP: time to progression
TTR: time to treatment response
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Boutsikou 2013	Only people surviving at 1 year were tested for EGFR mutation status
Crino 2008	EGFR expression tested only
ECOG 4508	Insufficient robust EGFR M+ samples available in trial
FASTACT	Data for the 7 EGFR participants not in usable format
Gatzemeier 2003	EGFR expression tested only
Goss 2009	EGFR expression tested only
Heigener 2014	The number of EGFR M+ participants was considered to be too small for analysis
Hirsh 2011	TKI used in both trial arms

Study	Reason for exclusion
Janne 2012	TKI used in both trial arms
JO25567	TKI used in both trial arms
Lilenbaum 2008	EGFR expression tested only
Massuti 2014	TKI used in both trial arms
NEJ005 2014	TKI used in both trial arms
NEJ009	TKI used in both trial arms
Rosell 2004	EGFR expression tested only
Rosell 2008	EGFR expression tested only
Thatcher 2014	EGFR testing by IHC
White	Due to small sample size, survival analyses for participants with EGFR mutations were not determined
Xie 2015	TKI used in both trial arms
Yang 2015	TKI used in both trial arms

EGFR M+: epidermal growth factor receptor mutation positive
IHC: immunohistochemistry
TKI: tyrosine-kinase inhibitor

Characteristics of studies awaiting assessment *[ordered by study ID]*

INSPIRE

Methods	Open-label, randomised, international phase III trial
Participants	633 people with previously untreated stage IV non-squamous NSCLC
Interventions	Treatment arm (315 participants): necitumumab + pemetrexed and cisplatin Comparator arm (318 participants): pemetrexed and cisplatin Participants received either cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 of a 3-week cycle for a maximum of 6 cycles alone, or with necitumumab 800 mg on days 1 and 8. Necitumumab was continued after the end of chemotherapy until disease progression or unacceptable toxic effects
Outcomes	Primary outcome: OS Secondary outcomes: TTP (RECIST criteria), ORR, duration of response, QoL, AEs
Notes	Necitumumab continued to disease progression

TALENT

Methods	Placebo-controlled, randomised, international phase III trial
Participants	1159 people with histologically documented, unresectable, locally advanced, recurrent, or metastatic (stage IIIB/IV) NSCLC; age 18 years or over; ECOG PS 0 or 1
Interventions	Treatment arm (580 participants): erlotinib 150 mg/daily + cisplatin and gemcitabine Comparator arm (579 participants): placebo + cisplatin and gemcitabine Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 of each cycle. Treatment up to 6 cycles
Outcomes	Primary outcome: OS Secondary outcomes: TTP (RECIST criteria), ORR, duration of response, QoL, AEs
Notes	

TRIBUTE

Methods	Placebo-controlled, randomised, multicentre phase III trial conducted in the USA
Participants	1079 people with histologically documented stage IIIB/IV NSCLC; age 18 years or over; and ECOG PS 0 or 1
Interventions	Treatment arm (539 participants): erlotinib 150 mg/daily + paclitaxel and carboplatin Comparator arm (540 participants): placebo + paclitaxel and carboplatin Paclitaxel 200 mg/m^2 and carboplatin AUC 6 every 3 weeks until disease progression
Outcomes	Primary outcome: OS Secondary outcomes: TTP, ORR, AEs
Notes	

AE: adverse event
AUC: area under the curve
ECOG PS: Eastern Cooperative Oncology Group Performance Status
NSCLC: non-small cell lung cancer
ORR: overall response rate
OS: overall survival
QoL: quality of life
RECIST: Response Evaluation Criteria in Solid Tumors
TTP: time to progression

Characteristics of ongoing studies *[ordered by study ID]*

ARCHER

Trial name or title	ARCHER
Methods	Open-label phase III RCT conducted in Asia

ARCHER *(Continued)*

Participants	440 stage IIIB/IV NSCLC with at least 1 activating EGFR mutation
Interventions	Dacomitinib Gefitinib
Outcomes	Primary: PFS by independent radiological review Secondary: PFS by investigator assessment, OS, ORR, duration of response, safety, QoL
Starting date	April 2013
Contact information	
Notes	Estimated primary completion date: May 2015. ClinicalTrials.gov identifier: NCT01774721. http://clinicaltrials.gov/show/NCT01774721

EGFR: epidermal growth factor receptor
NSCLC: non-small cell lung cancer
ORR: overall response rate
OS: overall survival
PFS: progression-free survival
QoL: quality of life
RCT: randomised controlled trial

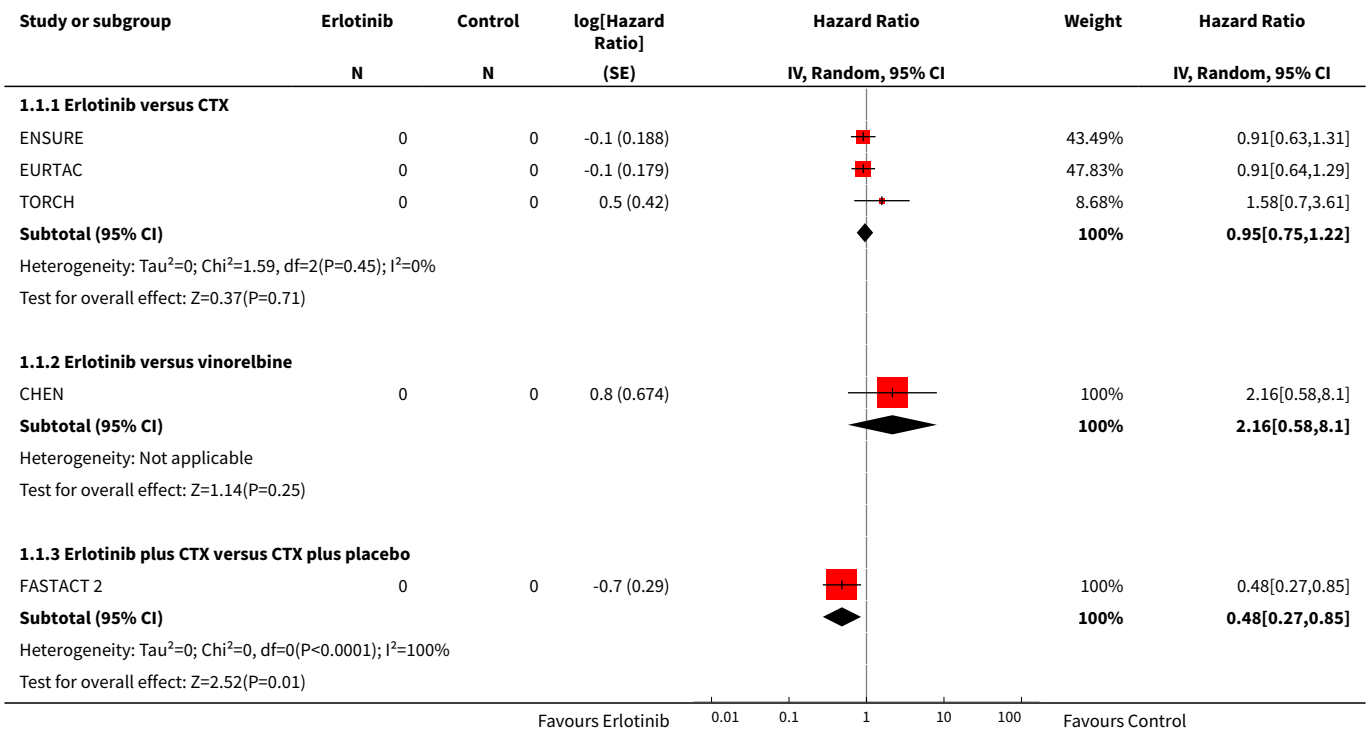
DATA AND ANALYSES

Comparison 1. Erlotinib versus control

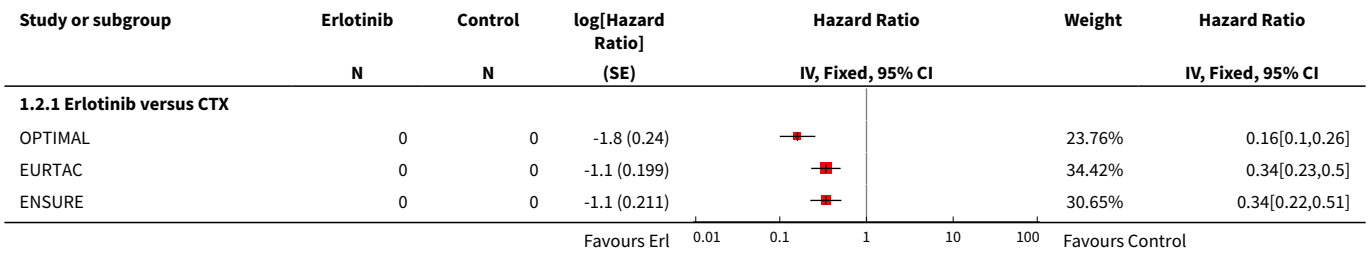
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	5		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Erlotinib versus CTX	3		Hazard Ratio (Random, 95% CI)	0.95 [0.75, 1.22]
1.2 Erlotinib versus vinorelbine	1		Hazard Ratio (Random, 95% CI)	2.16 [0.58, 8.10]
1.3 Erlotinib plus CTX versus CTX plus placebo	1		Hazard Ratio (Random, 95% CI)	0.48 [0.27, 0.85]
2 Progression-free survival	6		Hazard Ratio (Fixed, 95% CI)	Subtotals only
2.1 Erlotinib versus CTX	4		Hazard Ratio (Fixed, 95% CI)	0.30 [0.24, 0.38]
2.2 Erlotinib versus vinorelbine	1		Hazard Ratio (Fixed, 95% CI)	0.55 [0.21, 1.46]
2.3 Erlotinib plus CTX versus CTX plus placebo	1		Hazard Ratio (Fixed, 95% CI)	0.25 [0.16, 0.39]
3 Tumour response	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

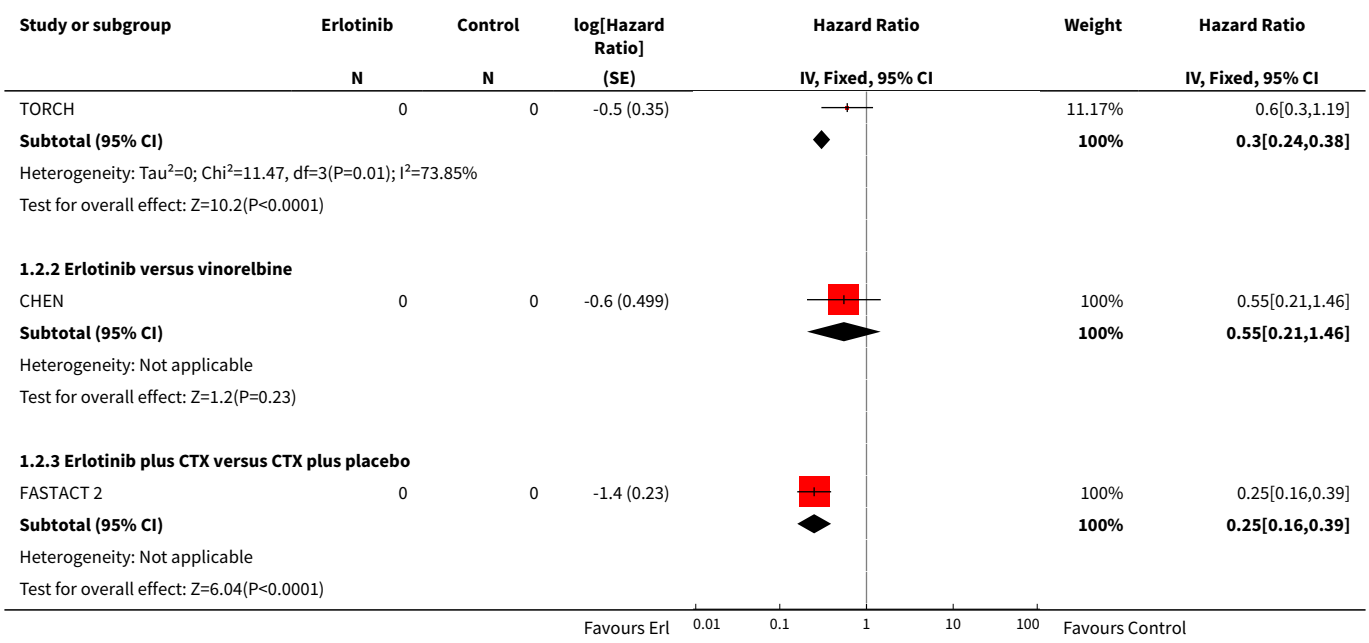
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Erlotinib versus CTX	5	593	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.85, 2.76]
3.2 Erlotinib versus vinorelbine	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.19, 3.67]
3.3 Erlotinib versus erlotinib plus CTX	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Erlotinib plus CTX versus CTX plus placebo	1	97	Risk Ratio (M-H, Fixed, 95% CI)	5.74 [2.86, 11.50]

Analysis 1.1. Comparison 1 Erlotinib versus control, Outcome 1 Overall survival.

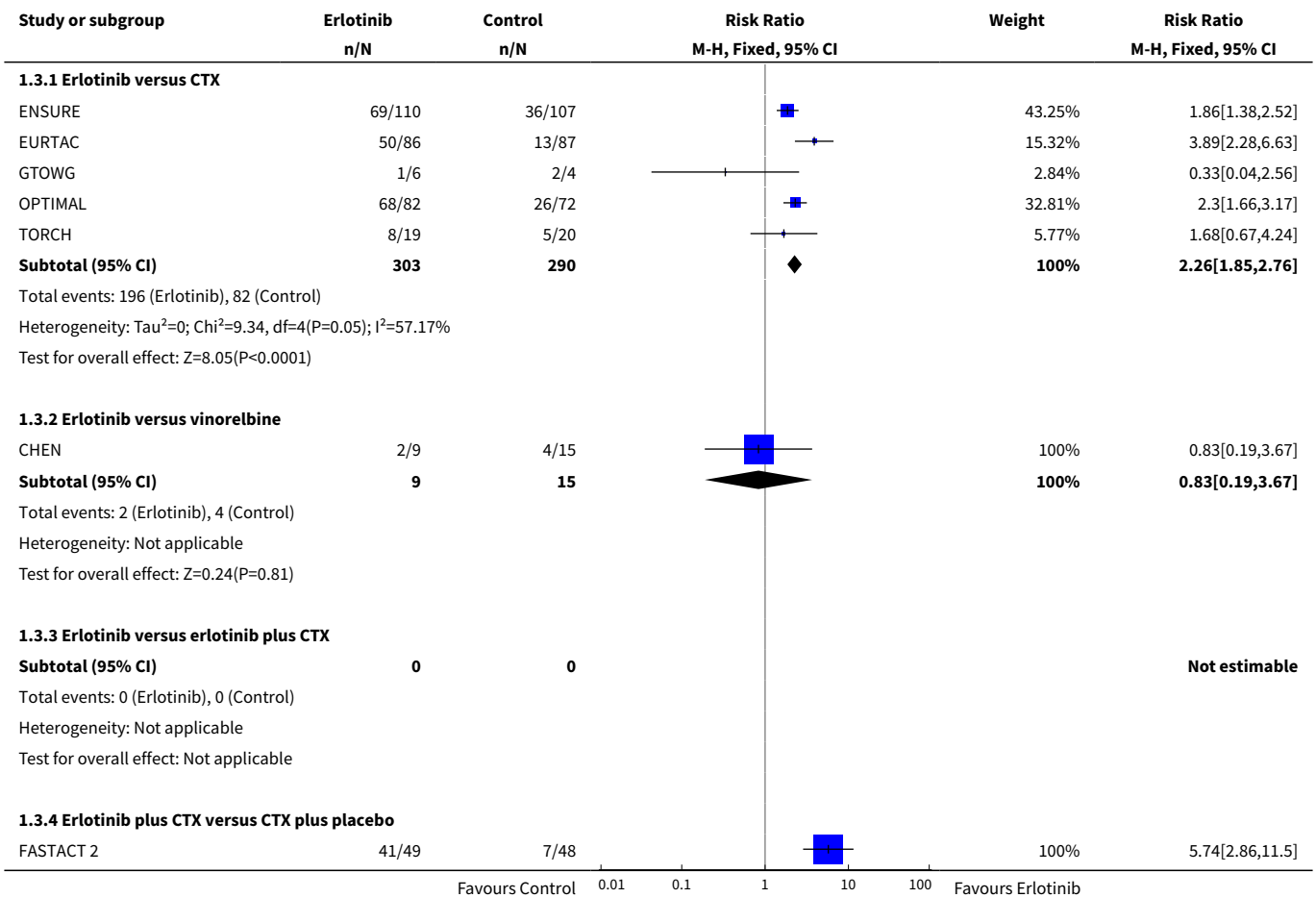


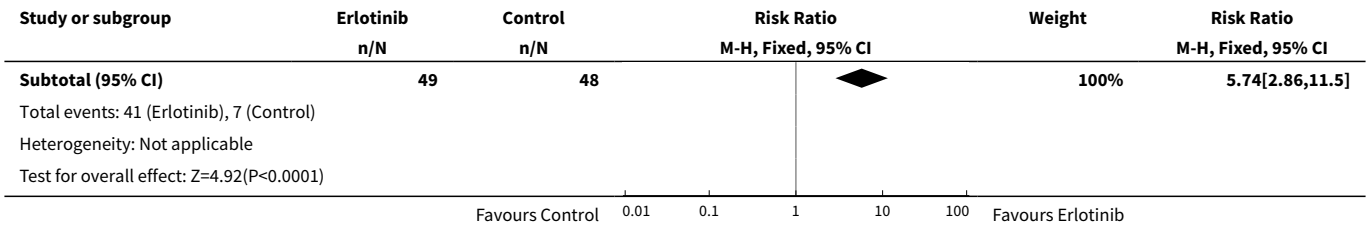
Analysis 1.2. Comparison 1 Erlotinib versus control, Outcome 2 Progression-free survival.





Analysis 1.3. Comparison 1 Erlotinib versus control, Outcome 3 Tumour response.



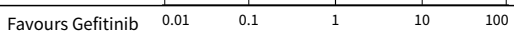


Comparison 2. Gefitinib versus CTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4		Hazard Ratio (Fixed, 95% CI)	Subtotals only
1.1 Gefitinib versus gemcitabine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	1.04 [0.50, 2.20]
1.2 Gefitinib versus paclitaxel plus carboplatin	2		Hazard Ratio (Fixed, 95% CI)	0.95 [0.77, 1.18]
1.3 Gefitinib versus docetaxel plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	1.25 [0.88, 1.78]
2 Progression-free survival	4		Hazard Ratio (Fixed, 95% CI)	Subtotals only
2.1 Gefitinib versus gemcitabine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.54 [0.27, 1.10]
2.2 Gefitinib versus paclitaxel plus carboplatin	2		Hazard Ratio (Fixed, 95% CI)	0.39 [0.32, 0.48]
2.3 Gefitinib versus docetaxel plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.49 [0.34, 0.71]
3 Tumour response	4	648	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.60, 2.19]
3.1 Gefitinib versus gemcitabine plus cisplatin	1	42	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.17, 4.34]
3.2 Gefitinib versus paclitaxel plus carboplatin	2	489	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.54, 2.18]
3.3 Gefitinib versus docetaxel plus cisplatin	1	117	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.26, 2.94]

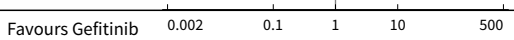
Analysis 2.1. Comparison 2 Gefitinib versus CTX, Outcome 1 Overall survival.

Study or subgroup	Gefitinib N	CTX N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Gefitinib versus gemcitabine plus cisplatin						
First-SIGNAL	0	0	0 (0.38)		100%	1.04[0.5,2.2]
Subtotal (95% CI)					**100%**	**1.04[0.5,2.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.11(P=0.91)						
2.1.2 Gefitinib versus paclitaxel plus carboplatin						
IPASS	0	0	0 (0.14)		59.59%	1[0.76,1.32]
NEJSG	0	0	-0.1 (0.17)		40.41%	0.89[0.64,1.24]
Subtotal (95% CI)					**100%**	**0.95[0.77,1.18]**
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.59); I^2=0%						
Test for overall effect: Z=0.45(P=0.65)						
2.1.3 Gefitinib versus docetaxel plus cisplatin						
WJTOG3405	0	0	0.2 (0.178)		100%	1.25[0.88,1.78]
Subtotal (95% CI)					**100%**	**1.25[0.88,1.78]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.26(P=0.21)						

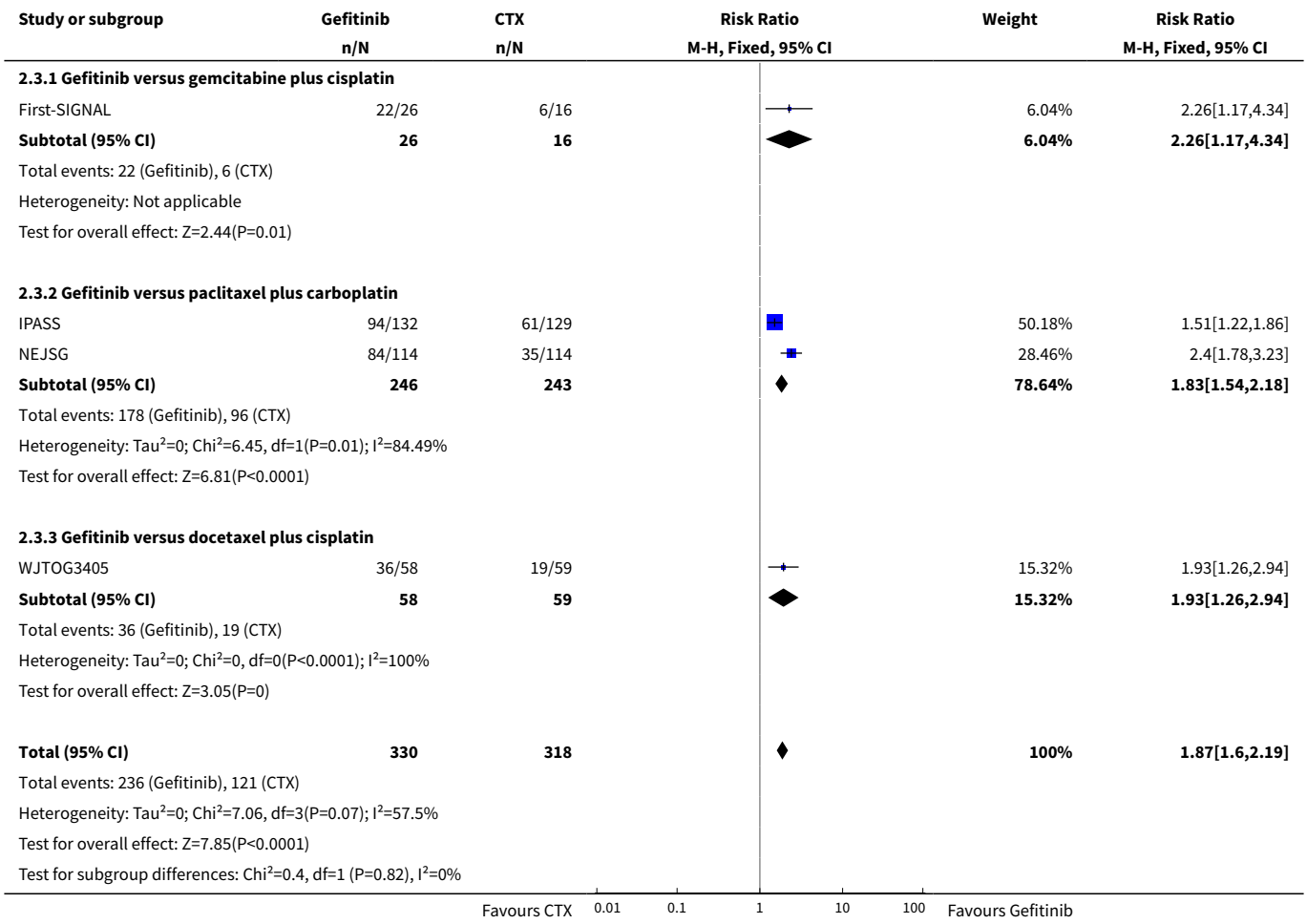


Analysis 2.2. Comparison 2 Gefitinib versus CTX, Outcome 2 Progression-free survival.

Study or subgroup	Gefitinib N	CTX N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.2.1 Gefitinib versus gemcitabine plus cisplatin						
First-SIGNAL	0	0	-0.6 (0.36)		100%	0.54[0.27,1.1]
Subtotal (95% CI)					**100%**	**0.54[0.27,1.1]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.69(P=0.09)						
2.2.2 Gefitinib versus paclitaxel plus carboplatin						
IPASS	0	0	-0.7 (0.15)		50%	0.48[0.36,0.65]
NEJSG	0	0	-1.1 (0.15)		50%	0.32[0.24,0.43]
Subtotal (95% CI)					**100%**	**0.39[0.32,0.48]**
Heterogeneity: Tau^2=0; Chi^2=3.74, df=1(P=0.05); I^2=73.23%						
Test for overall effect: Z=8.82(P<0.0001)						
2.2.3 Gefitinib versus docetaxel plus cisplatin						
WJTOG3405	0	0	-0.7 (0.19)		100%	0.49[0.34,0.71]
Subtotal (95% CI)					**100%**	**0.49[0.34,0.71]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.79(P=0)						



Analysis 2.3. Comparison 2 Gefitinib versus CTX, Outcome 3 Tumour response.

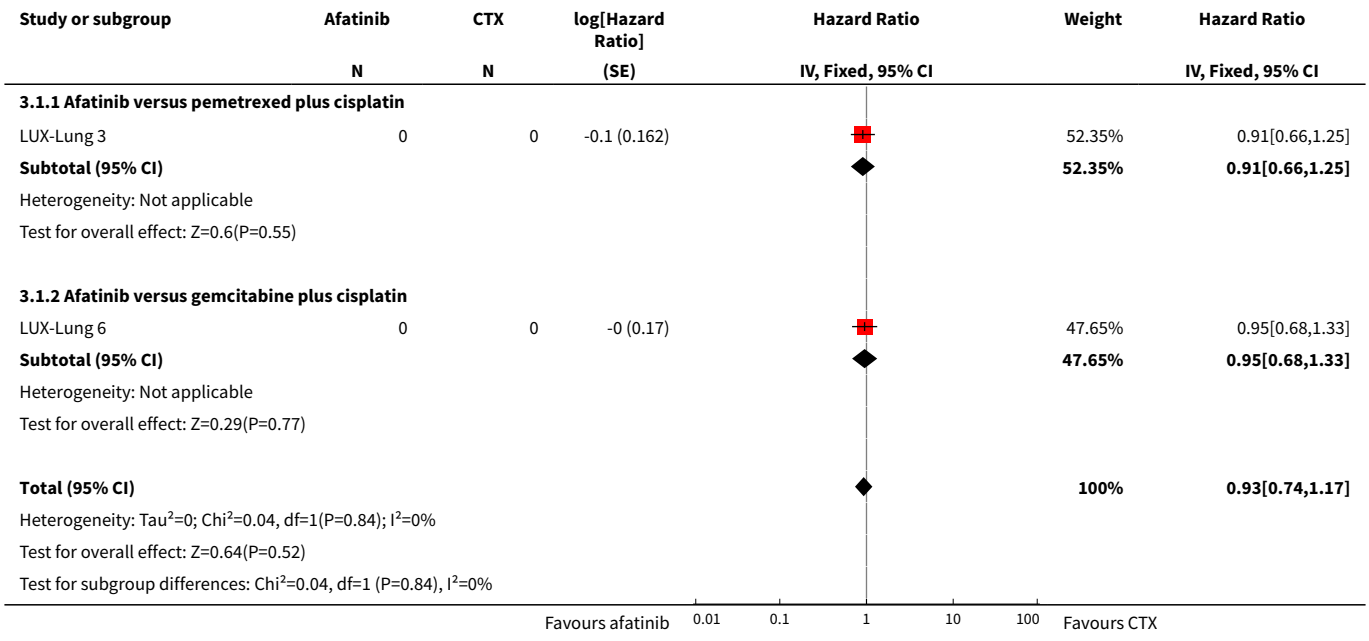


Comparison 3. Afatinib versus CTX

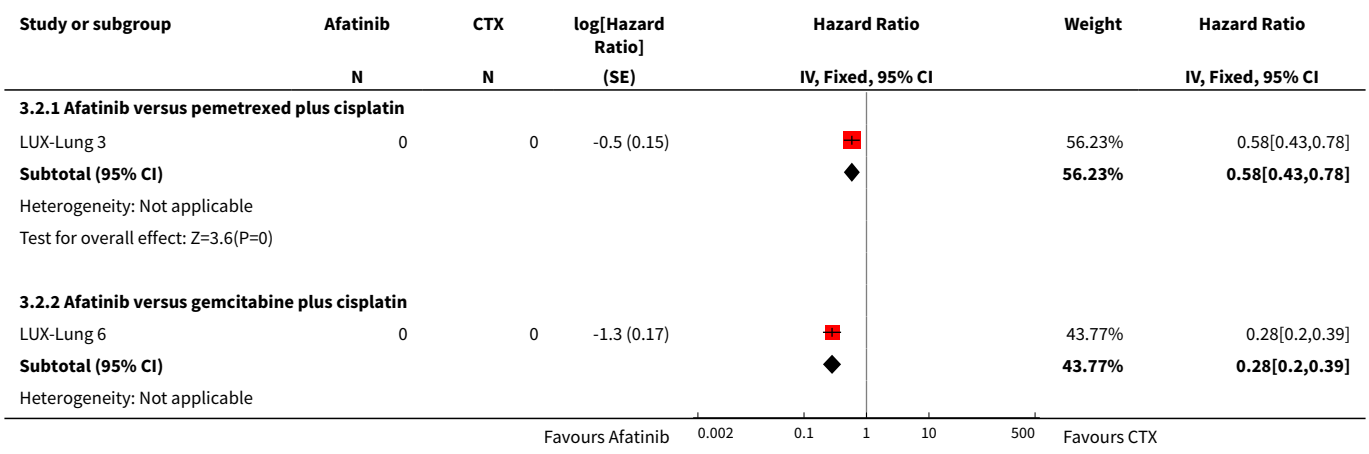
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2		Hazard Ratio (Fixed, 95% CI)	0.93 [0.74, 1.17]
1.1 Afatinib versus pemetrexed plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.91 [0.66, 1.25]
1.2 Afatinib versus gemcitabine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.95 [0.68, 1.33]
2 Progression-free survival	2		Hazard Ratio (Fixed, 95% CI)	0.42 [0.34, 0.53]
2.1 Afatinib versus pemetrexed plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.58 [0.43, 0.78]
2.2 Afatinib versus gemcitabine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.28 [0.20, 0.39]

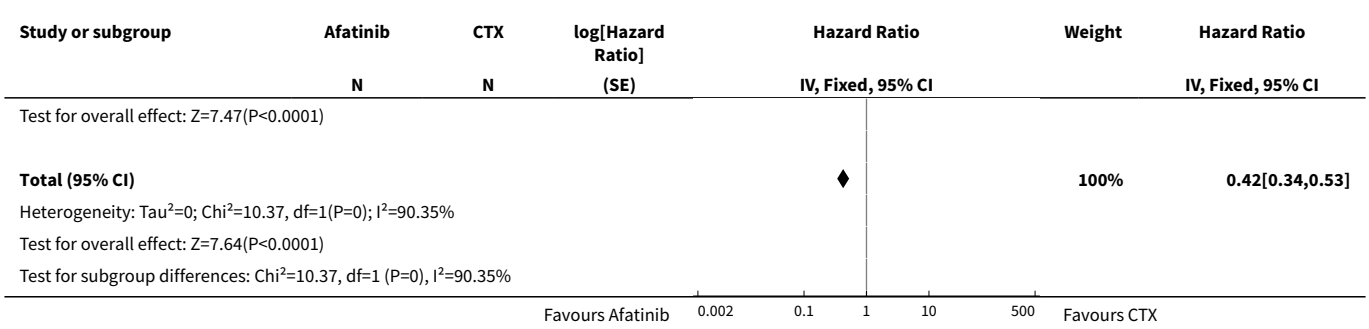
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Tumour response	2	709	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [2.12, 3.46]
3.1 Afatinib versus pemetrexed plus cisplatin	1	345	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.74, 3.54]
3.2 Afatinib versus gemcitabine plus cisplatin	1	364	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [2.08, 4.09]

Analysis 3.1. Comparison 3 Afatinib versus CTX, Outcome 1 Overall survival.

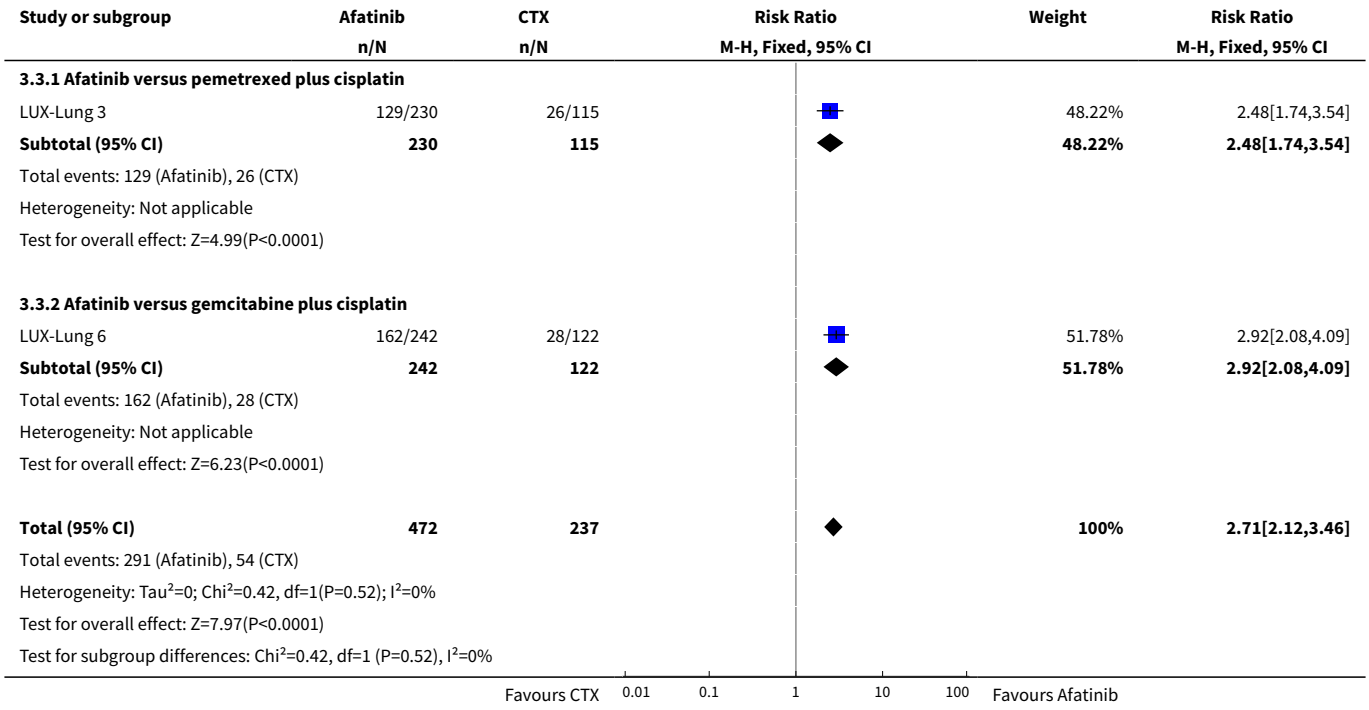


Analysis 3.2. Comparison 3 Afatinib versus CTX, Outcome 2 Progression-free survival.





Analysis 3.3. Comparison 3 Afatinib versus CTX, Outcome 3 Tumour response.

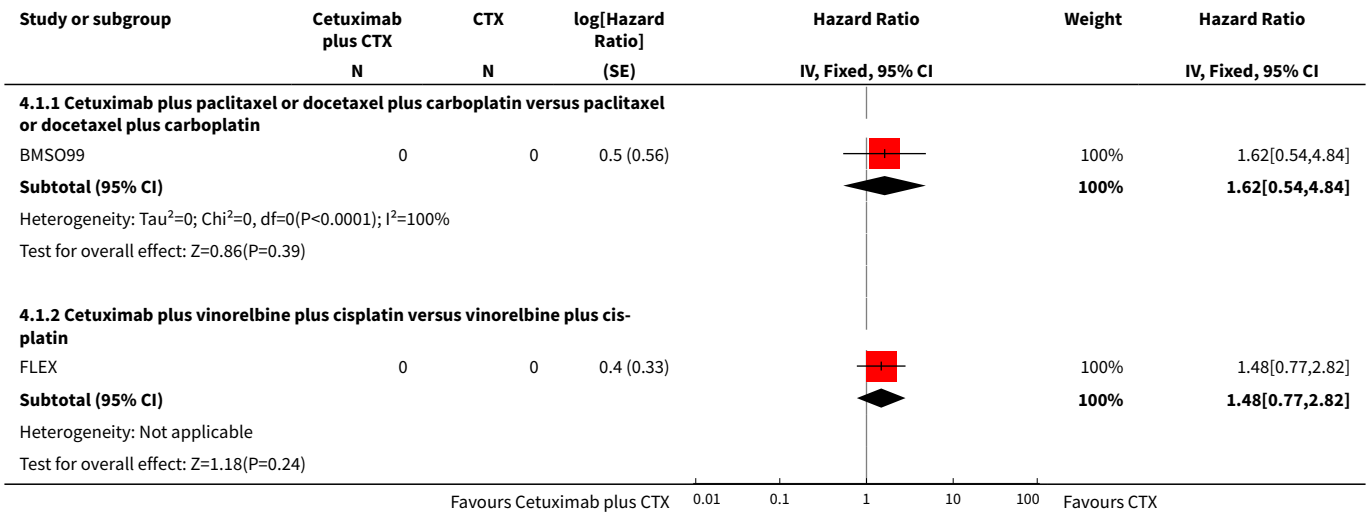


Comparison 4. Cetuximab plus CTX versus CTX

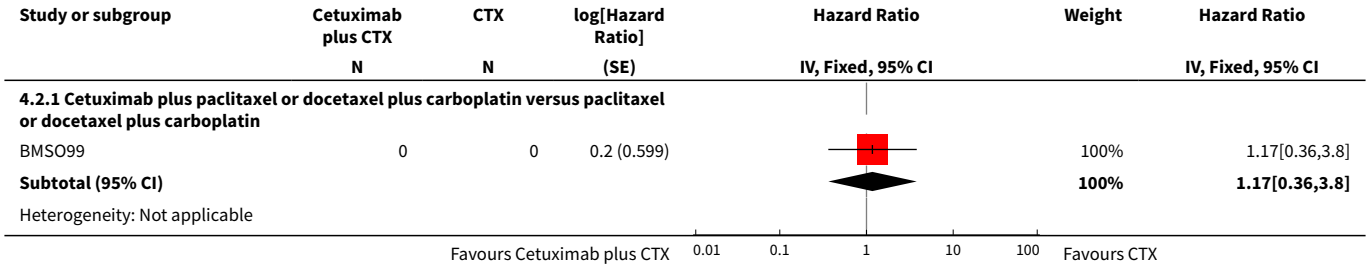
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
1.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1		Hazard Ratio (Fixed, 95% CI)	1.62 [0.54, 4.84]
1.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	1.48 [0.77, 2.82]

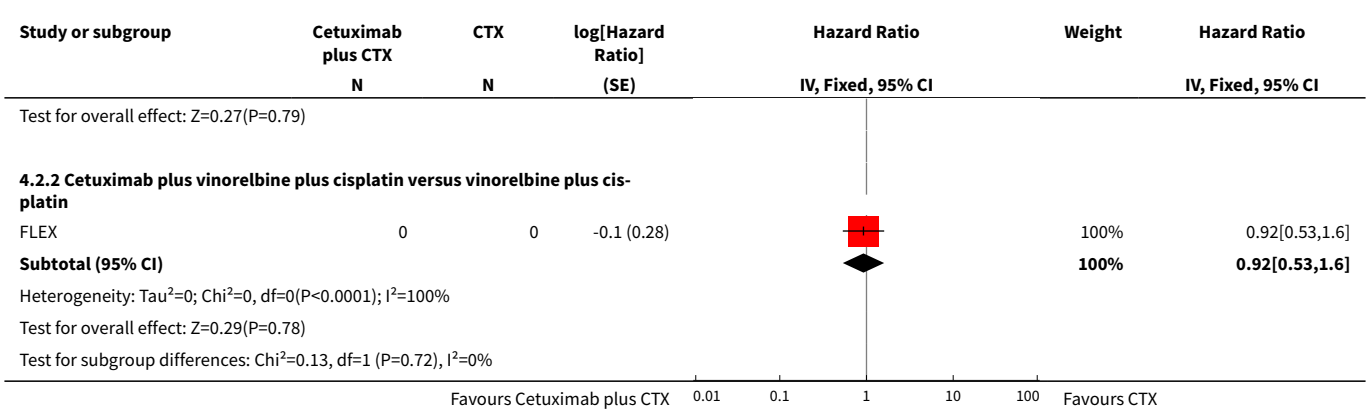
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Progression-free survival	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
2.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1		Hazard Ratio (Fixed, 95% CI)	1.17 [0.36, 3.80]
2.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1		Hazard Ratio (Fixed, 95% CI)	0.92 [0.53, 1.60]
3 Tumour response	2	81	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.83, 2.47]
3.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1	17	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.63, 32.38]
3.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.67, 2.11]

Analysis 4.1. Comparison 4 Cetuximab plus CTX versus CTX, Outcome 1 Overall survival.

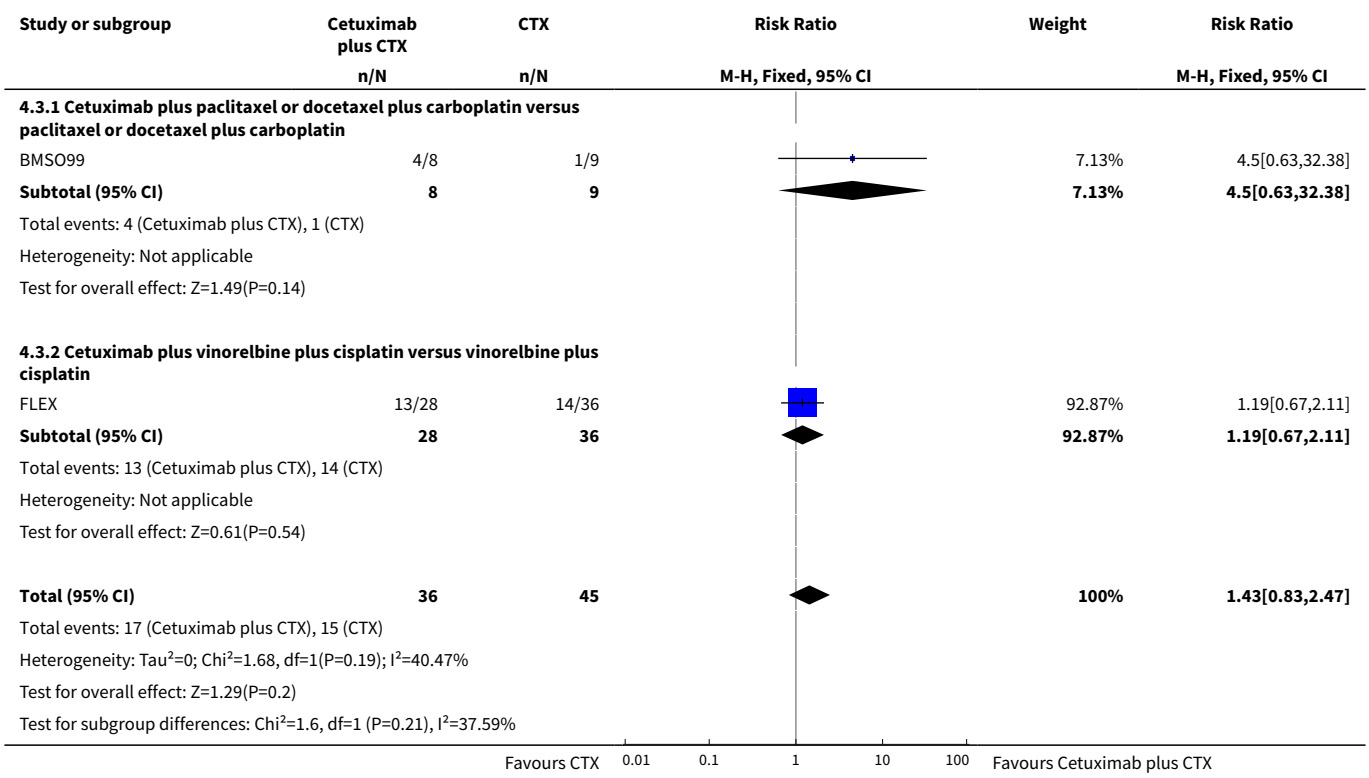


Analysis 4.2. Comparison 4 Cetuximab plus CTX versus CTX, Outcome 2 Progression-free survival.





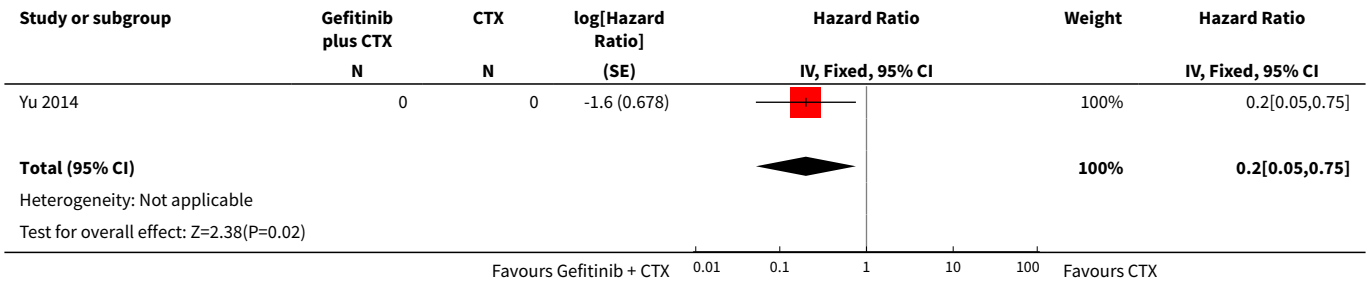
Analysis 4.3. Comparison 4 Cetuximab plus CTX versus CTX, Outcome 3 Tumour response.



Comparison 5. Gefitinib plus CTX versus CTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression-free survival	1		Hazard Ratio (Fixed, 95% CI)	0.20 [0.05, 0.75]

Analysis 5.1. Comparison 5 Gefitinib plus CTX versus CTX, Outcome 1 Progression-free survival.



ADDITIONAL TABLES

Table 1. Adverse events - most commonly occurring grade 3 & 4

Study	Definition of AE	Population	Top AE (listed according to intervention)	Second top AE (listed according to intervention)	Third top AE (listed according to intervention)	Top 3 AEs (listed according to comparator)
Afatinib trials						
LUX-Lung 3	Grade >= 3 CTC (V3) AEs that were reported in > 10% of participants in either group and if there was a >= 10% difference between the groups	EGFR M+ only	Rash/acne: 16.2% (AFA) vs 0% (cytotoxic chemotherapy)	Diarrhoea: 14.4% (AFA) vs 0% (cytotoxic chemotherapy)	Paronychia: 11.4% (AFA) vs 0% (cytotoxic chemotherapy)	Neutropenia: 18% vs 0.4% Fatigue: 12.6% vs 1.3% Leukopenia: 8.1% vs 0.4%
LUX-Lung 6	CTC (V3) Events are included if reported for >= 1% of participants in any treatment group	EGFR M+ only	Rash/acne: 14.6% (AFA) vs 0% (cytotoxic chemotherapy)	Diarrhoea: 5.4% (AFA) vs 0% (cytotoxic chemotherapy)	Stomatitis/mucositis: 5.4% (AFA) vs 0% (cytotoxic chemotherapy)	Neutropenia: 26.5% vs 0.4% Vomiting: 19.4% vs 0.8% Leukopenia: 15.1% vs 0.4%
Erlotinib trials						
CHEN	Incidence rate >= 10%	Unselected population	Rash: 64.9% (ERL) vs NR (cytotoxic chemotherapy)	Diarrhoea: 29.8% (ERL) vs NR (cytotoxic chemotherapy)	Mouth ulceration: 14% (ERL) vs NR (cytotoxic chemotherapy)	Anorexia: 26.3% vs NR Diarrhoea: 12.3% vs NR

Table 1. Adverse events - most commonly occurring grade 3 & 4 *(Continued)*

						Vomiting: 10.5% vs NR
ENSURE	Grade ≥ 3 ≥ 5% in either arm	EGFR M+ only	Rash: 6.4% (ERL) vs 1% (cytotoxic chemotherapy)	Neutropenia, leukopenia, anaemia: All 0.9% (ERL) vs 25%, 14.4%, 12.5% respectively (cytotoxic chemotherapy)	-	Neutropenia: 25% vs 0.9% Leukopenia: 14.4% vs 0.9% Anaemia: 12.5% vs 0.9%
EURTAC	Grade 3/4 CTC (V3) Common AEs	EGFR M+ only	Rash: 13% (ERL) vs 0% (cytotoxic chemotherapy)	Fatigue: 6% (ERL) vs 20% (cytotoxic chemotherapy)	Diarrhoea: 5% (ERL) vs 0% (cytotoxic chemotherapy)	Neutropenia: 22% vs 0% Fatigue: 20% vs 6% Thrombocytopenia: 14% vs 0%
FASTACT 2	Grade 3/4 CTC (V3) Most commonly reported	Unselected population	Neutropenia: 29% (ERL) vs 25% (cytotoxic chemotherapy)	Thrombocytopenia 14% (ERL) vs 14% (cytotoxic chemotherapy)	Anaemia: 11% (ERL) vs 9% (cytotoxic chemotherapy)	Neutropenia: 25% vs 29% Thrombocytopenia: 14% vs 14% Anaemia: 9% vs 11%
GTOWG	Grade 3/4	Unselected population	Rash: 12% (ERL) vs 0% (cytotoxic chemotherapy)	Diarrhoea: 6% (ERL) vs 2% (cytotoxic chemotherapy)	Constitutional symptoms: 3% (ERL) vs 5% (cytotoxic chemotherapy)	Neutropenia: 36% vs 0% Leukocytes: 33% vs 0% Haemoglobin: 11% vs 0.7%
OPTIMAL	Grade 3/4 CTC (V3) AEs occurred in 3% or more in either treatment group	EGFR M+ only	Increased ALT: 4% (ERL) vs 1% (cytotoxic chemotherapy)	Skin rash: 2% (ERL) vs 0% (cytotoxic chemotherapy)	Diarrhoea: 1% (ERL) vs 0% (cytotoxic chemotherapy)	Neutropenia: 42% vs 0% Thrombocytope-

Table 1. Adverse events - most commonly occurring grade 3 & 4 *(Continued)*

						nia: 40% vs 0% Anaemia: 13% vs 0%
TOPICAL	CTC (V3) Specific AEs grade 3 or 4	Unselected population	Dyspnoea: 59% (ERL) vs 64% (PLA)	Fatigue: 23% (ERL) vs 23% (PLA)	Diarrhoea: 8% (ERL) vs 1% (cytotoxic chemotherapy)	Dyspnoea: 64% vs 59% Fatigue: 23% vs 23% Anorexia: 5% vs 5%
TORCH	Worst toxicity experienced with first-line treatment alone	Unselected population	Skin rash: 11% (ERL) vs 0% (cytotoxic chemotherapy)	Pulmonary toxicity: 9% (ERL) vs 6% (cytotoxic chemotherapy)	Fatigue: 8% (ERL) vs 12% (cytotoxic chemotherapy)	Neutropenia: 21% vs 0% Thrombocytopenia: 12% vs 0% Fatigue: 12% vs 8%
Gefitinib trials						
First-SIGNAL	Grade 3 or 4 CTC (V3)	Unselected population	Rash: 29.3% (GEF) vs 2% (cytotoxic chemotherapy)	Anorexia: 13.8% (GEF) vs 57.3% (cytotoxic chemotherapy)	AST: 11.3% (GEF) vs 2% (cytotoxic chemotherapy)	Anorexia: 57.3% vs 13.9% Neutropenia: 54% vs 1.9% Fatigue: 45.3% vs 10.1%
INTACT 1	Grade 3/4 CTC Commonly occurring AEs	Unselected population	Thrombocytopenia*: 5.8% (GEF + cytotoxic chemotherapy) vs 5.6% (cytotoxic chemotherapy)	Rash: 3.6% (GEF + cytotoxic chemotherapy) vs 1.1% (cytotoxic chemotherapy)	Diarrhoea: 3.6% (GEF + cytotoxic chemotherapy) vs 2.3% (cytotoxic chemotherapy)	Thrombocytopenia*: 5.6% vs 5.8% Leukopenia: 2.5% vs 3.3% Diarrhoea: 2.3% vs 3.6%

Table 1. Adverse events - most commonly occurring grade 3 & 4 *(Continued)*

INTACT 2	Grade 3/4 CTC (V2) Common drug-related AEs	Unselected population	Diarrhoea: 9.9% (GEF + cytotoxic chemotherapy) vs 2.9% (cytotoxic chemotherapy)	Neutropenia: 6.7% (GEF + cytotoxic chemotherapy) vs 5.9% (cytotoxic chemotherapy)	Rash: 3.2% (GEF + cytotoxic chemotherapy) vs 1.5% (cytotoxic chemotherapy)	Neutropenia: 5.9% vs 6.7% Diarrhoea: 2.9% vs 9.9% Vomiting: 2.3% vs 2%
IPASS	Grade 3, 4, or 5 CTC (V3) At least 10% of participants in either treatment group and at least a 5% difference between arms	Unselected population	Diarrhoea: 3.8% (GEF) vs 1.4% (cytotoxic chemotherapy)	Any neutropenia: 3.7% (GEF) vs 67.1% (cytotoxic chemotherapy)	Rash: 3.1% (GEF) vs 0.8% (cytotoxic chemotherapy)	Any neutropenia: 67.1% vs 3.7% Leukopenia: 35% vs 1.5% Anaemia: 10.6% vs 2.2%
NEJSG	Grade >= 3 CTC (V3) At least 10% of participants in either treatment group and at least a 5% difference between arms	EGFR M+ only	ATE: 26.3% (GEF) vs 0.9% (cytotoxic chemotherapy)	Rash: 5.3% (GEF) vs 2.7% (cytotoxic chemotherapy)	Appetite loss: 5.3% (GEF) vs 6.2% (cytotoxic chemotherapy)	Neutropenia: 65.5% vs 0.9% Arthralgia: 7.1% vs 0.9% Neuropathy: 6.2% vs 0% Appetite loss: 6.2% vs 5.3%
WJ-TOG3405	Grade >= 3 CTC (V3) AEs occurred in 10% of either of the treatment groups	EGFR M+ only	ALT/AST: 27.5% (GEF) vs 2.3% (cytotoxic chemotherapy)	Rash: 2.3% (GEF) vs 0% (cytotoxic chemotherapy)	Fatigue: 2.3% (GEF) vs 2.3% (cytotoxic chemotherapy)	Neutropenia: 84% vs 0% Leucocytopenia: 50% vs 0% Anaemia: 17% vs 0%
Yu 2014	Grade 3+ Participants with at least 1 AE	Unselected population	Rash: 16% (GEF + cytotoxic chemotherapy) vs 0% (cytotoxic chemotherapy)	Vomiting: 10% (GEF) vs 8% (cytotoxic chemotherapy)	Neutropenia: 10% (GEF) vs 12% (cytotoxic chemotherapy)	Neutropenia: 12% vs 10% Nausea: 8% vs 5%

Table 1. Adverse events - most commonly occurring grade 3 & 4 *(Continued)*

						Vomiting: 8% vs 10%
Cetuximab trials						
BMSO99	Grade 3/4 CTC (V3) Most frequent and relevant grade 3/4 AEs	Unselected population	Neutropenia: 62.5% (CET + cytotoxic chemotherapy) vs 56% (cytotoxic chemotherapy)	Leukopenia: 43.8% (CET + cytotoxic chemotherapy) vs 30.7% (cytotoxic chemotherapy)	Fatigue: 15.1% (CET + cytotoxic chemotherapy) vs 12.2% (cytotoxic chemotherapy)	Same AEs as intervention
FLEX	Grade 3/4 CTC (V2) AEs that were reported in > 5% of participants (G3/G4) or > 1% (G4) or AEs of special interest in either group	EGFR M+ expressing	Neutropenia: 53% (CET + cytotoxic chemotherapy) vs 51% (cytotoxic chemotherapy)	Leukopenia: 25% (CET + cytotoxic chemotherapy) vs 19% (cytotoxic chemotherapy)	Febrile neutropenia: 22% (CET + cytotoxic chemotherapy) vs 15% (cytotoxic chemotherapy)	Neutropenia: 52% (cytotoxic chemotherapy) vs 52% CET + cytotoxic chemotherapy Leukopenia: 19% (cytotoxic chemotherapy) vs 25% (CET vs cytotoxic chemotherapy) Anaemia: 16% (cytotoxic chemotherapy) vs 1% (CET + cytotoxic chemotherapy)

AE: adverse event
AFA: afatinib
ATE: aminotransferase elevation
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CET: cetuximab
CTC: common toxicity criteria
ERL: erlotinib
EGFR M+: epidermal growth factor receptor mutation positive
GEF: gefitinib
NR: not reported
PLA: placebo
*Neutropenia was also reported as 5.8% for G3/4; as this rate was higher than the rate for all participants (5%) it was not included in the table.

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials, Issue 6 of 12, June 2015

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees

#2 lung:ti,ab

#3 (cancer* or carcin* or neoplasm* or tumour* or tumor*):ti,ab

#4 (non-small or nonsmall):ti,ab 4

#5 #2 and #3 and #4

#6 nsclc:ti,ab

#7 #1 or #5 or #6

#8 (tyrosine kinase inhibit* or monoclonal antibod* or EGFR or TKI*):ti,ab

#9 (erlotinib or tarceva):ti,ab

#10 (gefitinib or iressa):ti,ab

#11 (afatinib or gilotrif):ti,ab

#12 #8 or #9 or #10 or #11

#13 #7 and #12

Appendix 2. Ovid MEDLINE (R) from 1946 to 1 June 2015

1 exp Carcinoma, Non-Small-Cell Lung/

2 (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.

3 nsclc.ti,ab.

4 1 or 2 or 3

5 (tyrosine kinase inhibit$ or monoclonal antibod$ or EGFR or **TKI$**).tw.

6 (erlotinib or tarceva).af.

7 (gefitinib or iressa).af.

8 (afatinib or gilotrif).af.

9 5 or 6 or 7 or 8

10 4 and 9

11 randomized controlled trial.pt.

12 controlled clinical trial.pt.

13 randomized.ab.

14 placebo.ab.

15 drug therapy.fs.

16 randomly.ab.

17 trial.ab.

18 groups.ab.

19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20 exp animals/

21 humans.sh.

22 20 not 21

23 19 not 22

24 10 and 23

25 10 and 23

Appendix 3. Ovid EMBASE from 1980 to 1 June 2015

1 exp lung non small cell cancer/

2 (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.

3 nsclc.ti,ab.

4 1 or 2 or 3

5 (tyrosine kinase inhibit$ or monoclonal antibod$ or EGFR or TKI$).tw.

6 (erlotinib or tarceva).af.

7 (gefitinib or iressa).af.

8 (afatinib or gilotrif).af.

9 5 or 6 or 7 or 8

10 4 and 9

11 random:.tw. or placebo:.mp. or double-blind:.mp.

12 10 and 11

13 10 and 11

Appendix 4. ISI Web of Science

Topic=(non small cell lung) AND Topic=((erlotinib or tarceva or gefitinib or iressa or tyrosine kinase inhibit* or monoclonal antibod* or EGFR)) AND Topic=(random*)

Timespan=All Years. Databases= Science Citation Index Expanded (SCI- EXPANDED): 1899-present; Conference Proceedings Citation Index-Science (CPCI-S): 1990-present. Refined by: Document Types=(Article Or Meeting Abstract Or Review Or Proceedings Paper)

CONTRIBUTIONS OF AUTHORS

All review authors listed below contributed to the text or data sections, or both, and analysis. All review authors took part in the editing and production of the review.

J Greenhalgh: project co-ordination, data extraction, report writing

K Dwan: statistical advisor

A Boland: project management

V Bates: data extraction, entry, and analysis

F Vecchio: searching, data extraction, entry, and analysis

Y Dundar: searching, article screening

P Jain: clinical review

JA Green: input into all aspects of the review

DECLARATIONS OF INTEREST

Pooja Jain has received sponsorship from Eli Lilly, Roche Ltd, Pierre Fabre, and Boehringer Ingelheim to attend conferences. She received payment from Eli Lilly, Roche (who markets erlotinib) and Boehringer Ingelheim (who markets afatinib) to attend advisory boards until 2012.

All other authors have no declarations of interest.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have amended the wording of the protocol with respect to Types of interventions. We added a further exclusion to clarify that we would not consider trials with a targeted therapy in both arms. During the course of the review, we considered that the wording of the protocol was ambiguous in this respect.

We added three 'Summary of findings' tables including the gefitinib, erlotinib, and afatinib results for the outcomes overall survival and progression-free survival.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mutation; Afatinib; Antineoplastic Agents [adverse effects] [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; Carcinoma, Non-Small-Cell Lung [*drug therapy] [genetics] [mortality]; Cetuximab [adverse effects] [therapeutic use]; ErbB Receptors [*genetics]; Erlotinib Hydrochloride [adverse effects] [therapeutic use]; Gefitinib; Lung Neoplasms [*drug therapy] [genetics] [mortality]; Protein Kinase Inhibitors [therapeutic use]; Quality of Life; Quinazolines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male