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

Review information

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What's new

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History

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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 15-20%of non-squamous tumours. This subtype is more common in women than men, is less associated with smoking and has an improved prognosis compared to the M- subtypes.

Objectives

To assess the clinical effectiveness of single or combination EGFR therapies used in the first-line treatment of patients with locally advanced or metastatic EGFR M+ NSCLC compared with other cytotoxic chemotherapy (CTX) agents, or best supportive care (BSC). The primary outcome is overall survival.

Search methods

We conducted electronic searches of the databases of The Cochrane Library (to 1st June 2015), MEDLINE (1946 to 1st June 2015), EMBASE (1980 to 1st June 2015), ISI Web of Science (1899 to 1st June 2015). In addition we searched the conference abstracts of ASCO and ESMO. Evidence Review Group submissions to NICE were also searched as were the

references 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 best supportive care (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 authors independently identified articles, extracted data and carried out risk of bias assessments. Meta-analyses were conducted using a fixed effect model unless there was substantial heterogeneity when a random effects analysis was also performed as a sensitivity analysis.

Main results

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

Erlotinib was the intervention treatment in 8 trials, gefitinib in 7 trials, afatinib in 2 trials and cetuximab in 2 trials. Overall survival (OS) data showed inconsistent results between the included trials that compared EGFR targeted treatments against CTX or placebo. The findings of one trial (FASTACT 2) did report a statistically significant OS gain for patients treated with erlotinib plus CTX when compared to CTX alone but this result was based on a small number of patients (n=97). For progression-free survival (PFS), a pooled analysis of three trials (n=378) demonstrated a statistically significant benefit for erlotinib compared with CTX (HR=0.30; 95% CI: 0.23 to 0.40).

In a pooled analysis with 491 patients with gefitinib, two trials (IPASS; NEJSG) demonstrated a statistically significant PFS benefit of gefitinib compared with CTX (HR=0.39; 95% CI:0.32 to 0.48).

Afatinib (n=709) showed a statistically significant benefit when compared with chemotherapy in a pooled analysis of two trials (HR= 0.42; 95% CI: 0.34 to 0.53). Commonly reported adverse events for afatinib, erlotinib and gefitinib monotherapy were rash and diarrhoea.

No statistically significant PFS benefit for cetuximab plus CTX (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, two trials showed improvement in one or more indices for the TKI compared to chemotherapy.

The risk of bias was mixed, with lack of blinding being the main reason the majority of trial were classified as at unclear risk of bias.

Authors' conclusions

Erlotinib, gefitinib or afatinib are all active agents in EGFR M+ NSCLC patients, and demonstrate an increased response rate and prolonged progression-free survival compared to cytotoxic chemotherapy . Cytotoxic chemotherapy is less effective in this subtype than erlotinib, gefitinib or afatinib and is associated with greater toxicity. There is no data supporting monoclonal antibody therapy.

Plain language summary

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

Background

Lung cancer is the most common cancer in the world. It tends to be diagnosed in older people and because it is has few symptoms is usually diagnosed at a late stage of the disease.

The most common type of lung cancer is non-small cell lung (NSCLC) cancer which affects specific cells in the lungs. Around 15-20% of people with NSCLC will have a specific type of disease known as epidermal growth factor receptor positive (EGFR M+) . People who have EGFR M+ NSCLC usually do not respond to standard treatment with chemotherapy. New treatments which can target EGFR M+ NSCLC have recently been developed and licensed and their efficacy is assessed in this review.

Objectives

The purpose of this review is to assess whether treatments targeted at EGFR M+ NSCLC have any benefit in survival or quality of life compared to standard chemotherapy.

Trial Characteristics

We identified 19 trials that investigated four different EGFR-targeted drugs, comprising the tyrosine kinase inhibitors afatinib, erlotinib and gefitinib, and the antibody cetuximab. Trials which presented results up to June 2015 are included in this review.

Results

This review demonstrates that treatment with erlotinib, gefitinib and afatinib leads to increased time until disease progression compared to conventional or combined chemotherapy. However, there is no increase in overall survival when compared with standard chemotherapy except for one preplanned subgroup analysis for afatinib in patients with the codon 19 deletion.

There was no increase in delayed disease progression or survival when cetuximab is compared with standard chemotherapy.

Conclusion

Treatment with erlotinib, gefitinib and afatinib confer delayed disease progression but do not extend life. The side effects associated with erlotinib, gefitinib and afatinib are more favourable than those associated with conventional chemotherapy. Treatment with cetuximab in combination with chemotherapy is of no benefit in controlling these tumours or extending life.

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). Lung cancer is rarely diagnosed in people younger than 40 years of age and 90% of cases are identified in people over the age of 60 years (Cancer Research UK 2013). 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 approximately 84% of lung cancer cases and comprises two main histological subgroups, squamous cell carcinoma and non-squamous cell carcinoma (Schiller 2002). Squamous cell carcinoma accounts for 33% of all NSCLC cases whilst non-squamous cell carcinoma (including adenocarcinoma and large cell carcinoma) accounts for 29% of NSCLC cases. Approximately 16% of patients have NSCLC that is 'not-otherwise specified' with the diagnosis based on cytology alone (Schiller 2002). The prognosis for patients with metastatic NSCLC is poor, with a median survival of the order of 11 months (Schiller 2002).

Treatment for patients with NSCLC is dependent not only on the histological subtype and genetic subtype of the patient, but also on disease stage, co-morbidity, and performance status (PS). Chemotherapy for advanced disease can extend overall survival (OS) by several months compared to best supportive care (BSC) and may improve quality of life (QoL), but it may not be appropriate for many patients with poor PS (Spiro 2004;Brown 2013).

In recent years the clinical 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 dimerization and tyrosine kinase autophosphorylation, leading through signal transduction to cell proliferation (NCBI: Han 2012). It is estimated that 10% to 15% of patients with non-squamous NSCLC have tumours that are EGFR M+ (Peters 2012; Rosell 2012). An EGFR mutation frequency of 21% was reported by Shigematsu 2005 and is more frequently observed in never smokers than ever smokers (51% vs 10%), in adenocarcinomas vs cancers of other histologies (40% vs 3%), in patients of East Asian ethnicity vs other ethnicities (30% vs 8%), and in females vs males (42% vs 14%). Other trials have reported EGFR mutations (exons 18 to 21) in 17% to 20% of samples of NSCLC (Rosell 2009; Ulivi 2012) and these more frequently occur in never smoking females (Scoccianti 2012).

The identification of patients 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. The TKIs are orally administered agents while the MABs are given intravenously. Patients of interest to this review are chemotherapy-naive patients with locally advanced or metastatic (Stage IIIB or IV) EGFR M+ NSCLC who are 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. They are oral treatments (tablets) that are taken daily until the disease progresses. Other drugs, for example, the TKI dacomitinib and the MAB cetuximab, are therapies currently under clinical investigation but are not yet licensed for the first-line treatment of patients with EGFR M+ NSCLC.

In the UK, NICE 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 (ESMO) guidelines recommend first-line treatment with monotherapy afatinib, erlotinib or gefitinib (Peters 2012; Reck 2014). In the USA, the Food and Drug Administration (FDA) 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 patients with NSCLC, and the availability and quality control of mutation testing which determines patient selection.

Why it is important to do this review

Treatments for patients with NSCLC are evolving rapidly. Up until early 2000, patients with NSCLC were offered standard cytotoxic chemotherapy treatments (for example, docetaxel, vinorelbine, paclitaxel and gemcitabine), and in many cases given in two-drug combinations (Brown 2013). However, in recent years patients have been treated with drugs according to their disease histology (for example, pemetrexed for non-squamous disease). Even more recently, as understanding of

NSCLC has evolved, targeted treatments have been developed (for example,TKIs and MABs) to treat specific groups of patients based on molecular criteria. 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), but the prevalence is higher in Asian populations. It is, therefore, important to synthesise evidence for the clinical effectiveness and toxicity of these innovative 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 or combination EGFR therapies used in the first-line treatment of patients 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 is overall survival.

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, such as surgery or radical radiotherapy.

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 agents or combinations of cytotoxic chemotherapy without a targeted therapy in either arm, trials with targeted therapy in both arms and we did not evaluate maintenance or second-line strategies.

Types of outcome measures

Primary outcomes

Overall survival (OS)

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for relevant published literature up to June 2015. Searches were not restricted by language.

CENTRAL (Cochrane Central Register of Controlled Trials) (*The Cochrane Library*). June 2015
CDSR (Cochrane Database of Systematic Reviews). June 2015
DARE (Database of Abstracts of Reviews of Effectiveness).June 2015
EMBASE (OvidSP). June 2015
Health Technology Assessment (HTA) database.June 2015
ISI Web of Science - Proceedings (Index to Scientific & Technical Proceedings).June 2015
MEDLINE (accessed via PubMed and OvidSP). June 2015
ISI Web of Science - Science Citation Index Expanded.June 2015

We modified the search strategies over time. To ensure the integrity of the searches, the strategy outlined in Appendix 3 was re-run in PubMed from inception to June 2015 (overall) and we compared the results with the results of all other searches. Any non-duplicate articles were examined for possible inclusion in the review. The strategies used to explore MEDLINE (via Ovid) are outlined in Appendix 1; Appendix 2; Appendix 3 and we adapted these, as appropriate, for the remaining databases.

Searching other resources

Other resources we searched included: 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 (ASCO) and the European Society for Medical Oncology (ESMO) 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.

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). Firstly, review authors independently scanned the titles and abstracts of references identified by the search strategy. Full details of possibly relevant trials were obtained and assessed independently for inclusion in the review. If a disagreement occurred, the review authors attempted to reach a consensus by discussion, or by involving a third review author (AB and JG). Trials that did not meet all of the inclusion criteria were excluded and their bibliographic details listed with reasons for exclusion. Ongoing trials that did not report relevant data but met the inclusion criteria were listed for future use. For trials published in abstract form only, if it was clear that a trial was eligible then it was included. If it was not clear, authors were contacted for further information and the trial was placed in 'awaiting assessment' until a reply was received.

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 for 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* (Higgins 2011) (see domains listed below) Two reviewers (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 report 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.

Summary of findings tables are presented 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 present relative treatment effects in the form of relative risks (RR) with 95% confidence intervals (CI). For continuous outcomes, we calculated mean differences (MD) 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.¬Standardised mean differences (SMDs) were calculated for QoL 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, data were requested from authors.

All trials allowed patient crossover to another treatment after progression but there are no details regarding how this was dealt with in any of the analyses of OS.

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

Unit of analysis issues

We did not include cross-over trials in the review.

Dealing with missing data

We contacted authors (and sponsors) of trials for missing data.

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;, this 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 40%, heterogeneity might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity and
- 75% to 100%, considerable heterogeneity.

Assessment of reporting biases

If a sufficient number of trials are identified, a funnel plot can be constructed. If asymmetry is present in the funnel plot, possible causes of bias may be explored, such as heterogeneity or outcome reporting bias.

Data synthesis

We have summarised individual trial data in structured tables and as a narrative description. 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%) and used a random-effect model as a sensitivity analysis. In future versions of this review, if there is considerable heterogeneity (I^2 > 75%) we may combine data but conclusions will highlight the amount of heterogeneity present.

Indirect comparisons and network meta-analysis

In future versions of this review, if trials are identified that compare different interventions which are sufficiently similar in terms of their populations and outcomes, we may make indirect comparisons for competing interventions that have not been compared directly. Do we not need to be more specific about why we didn't do this while others have! Multiple treatment 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-effect model within STATA to conduct analyses using code from www.mtm.uoi.gr.

Transitivity (the trials making different direct comparisons must be sufficiently similar in all respects other than the treatments being compared) will be evaluated 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 is only considering first-line treatment, indications are similar.

Consistency will be evaluated using a loop specific approach (Salanti 2009) and design interaction consistency model (Higgins 2012) will also be used. If inconsistency is identified, the network meta-analysis will not be presented.

Estimates of treatment effect will be assessed by pairwise meta-analysis. Network meta-analysis will be conducted where appropriate.

Prior to analysis a diagram of the network for all relevant interventions will be drawn, indicating the number of trials per comparison. Ranking probabilities for each treatment will be derived and displayed using the Surface Under the Cumulative RAnking curve (SUCRA) plot and rankograms (Salanti 2011).

The possible effects of risk of bias on the clinical effectiveness data and review findings will be discussed.

Subgroup analysis and investigation of heterogeneity

In an update of this review, when sufficient trials are included and where data are available, subgroup analysis may be performed for the following subgroups:

- Smoking status: smoker, non-smoker;
- Age: < 65 years, age ≥ 65 years;
- Gender: male, female;
- Ethnicity: Asian, non-Asian;
- Performance status:0/1, 2/3.

Sensitivity analysis

In an update of this review, when sufficient srials are included, we will conduct sensitivity analyses based on the overall risk of bias of the included trials. Overall risk of bias will be based on sequence generation, allocation concealment and blinding (for the specific outcome), and the summary assessment will be based 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 7 records via hand-searching of reference lists and we found 2 other records from our search of conference abstracts. All of the potentially relevant references were screened and we included 19 eligible RCTs (reported in 55 publications) comparing EGFR targeted therapy to chemotherapy as first-line treatment in NSCLC patients in our review (Figure 1).

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

Included studies

The 19 trials (Characteristics of included studies) which met the inclusion criteria (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) were published or updated between 2003 and 2015. With the exception of GTOWG, all trials were published as peer-reviewed papers. The overall number of patients recruited to the trials ranged between 113 (CHEN) and 1217 (IPASS) with an overall trial population of 9414. The median length of follow up (where reported) ranged from 15.9 months (INTACT 1) to 59 months (WJTOG3405).

EGFR mutation status - overall population versus subgroups

Seven trials included EGFR M+ patients only (EURTAC; ENSURE; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405). The number of patients recruited to the EGFR M+ only trials ranged from 165 (OPTIMAL) to 364 (LUX-Lung 6) with a total population of 1672. The remaining 12 trials recruited a 'mixed' population of patients, that is patients were not selected for inclusion in the trial on the basis of their EGFR mutation status. These latter trials report results for the subgroup of patients with EGFR M+ mutation status only. The numbers of patients reported in these subgroups range from 10 (GTOWG) to 261(IPASS) with a combined total of 645. The combined total of patients with EGFR M+ NSCLC is 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 the remainder were conduced in America (BMSO99), Italy and Canada (TORCH), America and Europe (INTACT 2). LUX-Lung 3 , INTACT 1 and FLEX were international trials. The seven trials that recruited exclusively EGFR M+ patients were conducted in Asia (ENSURE; LUX-Lung 6; NEJSG; OPTIMAL; 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 (i.e. oral vs i.v. 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 (BMSO99; CHEN; ENSURE; EURTAC; FASTACT 2, First-SIGNAL; FLEX; INTACT 1; INTACT 2; IPASS; OPTIMAL; TOPICAL; TORCH; LUX-Lung 3; LUX-Lung 6) were partially or totally funded by a pharmaceutical company; the NEJSG and WJTOG3405 trials were funded by scientific groups. The funding source for the GTOWG and Yu 2014 trials is not reported.

Population characteristics

Data for age, sex, performance status (PS) and smoking status were provided for all trials except for the INTACT 1, INTACT 2 and GTOWG trials (no details of smoking history). The median age of the overall population of all the patients in the included trials ranged from 56 to 77 years; the median age of patients in the EGFR M+ only trials ranged from 56 to 65 years. Two trials (CHEN and GTOWG) only included patients aged over 70 years and NEJSG and Yu 2014 only reported mean age. There was a greater proportion of females in 9 of the trials (ENSURE; First-SIGNAL; IPASS; LUX-Lung 3; LUX-Lung 6; NEJSG; OPTIMAL; WJTOG3405; EURTAC), and greater prevalence of males in 7 trials (TORCH; CHEN; BMSO99; GTOWG; INTACT 1; INTACT 2 FLEX). The majority of patients were of good PS (ECOG or WHO 0 or 1). The GTOWG abstract did not report PS.

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). In FASTACT 2, erlotinib was used in combination with a platinum doublet containing gemcitabine.

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). In INTACT 1; INTACT 2; Yu 2014 gefitinib was used in combination with chemotherapy.

Afatinib

Two trials compared afatinib (n=709) with cytotoxic chemotherapy (LUX-Lung 3;LUX-Lung 6).

Cetuximab

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

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

Outcomes

The primary outcome for the majority of trials was progression-free survival (PFS) with secondary outcomes of overall survival (OS), tumour response rate, symptom palliation, quality of life (Qol) and safety. Overall survival was the primary outcome in 6 trials (First-SIGNAL; FLEX; INTACT 1; INTACT 2; TOPICAL; TORCH).

Excluded studies

We excluded 290 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. Other trials were excluded if they were designed to assess maintenance treatment or an EGFR- targeted therapy was used in by trial arms. We were not able to easily exclude articles at the screening stage as we could not be certain from the abstract whether subgroup analyses of outcomes of patients with EGFR M+ tumours were reported. In the Characteristics of excluded studies table we list trials that appear to meet the inclusion criteria, but on closer examination were not a complete match. Patients in 5 trials were not tested for EGFR mutations Crino 2008; ECOG 4508; Gatzemeier 2003; Goss 2009; Lilenbaum 2008, Two trials tested for EGFR expression only Rosell 2008;Thatcher 2014. In 3 trials there were too few patients with EGFR M+ tumours to warrant analysis FASTACT; Heigener 2014; White and in 8 trials TKI treatment was included in both trial arms Hirsh 2011; Janne 2012; JO25567; Massuti 2014; NEJ005 2014; NEJ009; Xie 2015; Yang 2015. One trial assessed the outcomes only of patients who survived at 1 year Boutsikou 2013 and in another trial there were insufficient samples available for testing ECOG 4508.

Risk of bias in included studies

Allocation (selection bias)

Of the 19 included trials, 11 reported adequate information about the methods used to generate the randomisation sequence and the allocation concealment procedure and these trials were considered to be at low risk of bias (EURTAC; FASTACT 2; FLEX; IPASS; LUX-Lung 3; LUX-Lung 6; TOPICAL; NEJSG; OPTIMAL; TORCH; WJTOG3405). For the remaining 8 trials, the risk of bias was considered to be unclear due to the lack of reported information (BMSO99; CHEN; ENSURE; First-SIGNAL; GTOWG; INTACT 1; INTACT 2; Yu 2014).

Blinding (performance bias and detection bias)

Performance bias

Only 4 of the 19 included trials reported employing blinding procedures (INTACT 1; INTACT 2; NEJSG; TOPICAL). The remainder were explicitly stated as being 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 (i.e. oral vs intravenous).

Detection bias

Eleven of the trials were considered to be at low risk of detection bias for the outcome of PFS as they incorporated independent verification procedures (EURTAC; ENSURE; FASTACT 2 First-SIGNAL; NEJSG; BMSO99; LUX-Lung 3;LUX-Lung 6) or blinded outcome assessment (INTACT 1; INTACT 2;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 PFS.

Incomplete outcome data (attrition bias)

In all trials, all patients 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 and therefore all trials were considered to be at low risk of bias.

Selective reporting (reporting bias)

Only one trial was considered to be at high risk of reporting bias (CHEN). The trial protocol stated time to progression as a primary outcome of the trial; however this outcome is not reported in the published paper. Two trials were considered to be at unclear risk of bias as there was insufficient information available to judge selective reporting (FLEX; GTOWG). All other trials were considered 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 (TORCH) was terminated early as the non-inferiority of the intervention arm was demonstrated by the first planned interim analysis. Two trials were terminated early for benefit (ENSURE; EURTAC).

Effects of interventions

Pairwise meta-analysis

Erlotinib vs Control-

Erlotinib vs gemcitabine plus carboplatin: One trial considered this comparison (OPTIMAL).

Erlotinib vs gemcitabine plus cisplatin: Two trials considered this comparison (ENSURE ; TORCH).

Erlotinib vs docetaxel plus cisplatin or gemcitabine plus cisplatin: One trial considered this comparison (EURTAC).

Erlotinib vs carboplatin plus vinorelbine: One trial considered this comparison (GTOWG).

Erlotinib vs vinorelbine: One trial considered this comparison (CHEN).

Erlotinib plus gemcitabine plus carboplatin or cisplatin vs gemcitabine plus carboplatin or cisplatin plus placebo: One trial considered this comparison (FASTACT 2).

Erlotinib vs placebo: One trial considered this comparison (TOPICAL).

Primary outcome: Overall survival

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

The pooled treatment effect estimate for three trials, (HR of 0.95 (95% CI: 0.65, 1.66, I^2=0, 3 trials)indicated no significant difference in OS between the groups (EURTAC;TORCH; ENSURE). CHEN reported a HR of 2.16 (95% CI: 0.58, 8.10) for OS comparing erlotinib vs vinorelbine in elderly patients, indicating no significant difference in OS between the groups. FASTACT 2 reported a HR of 0.48 (95% CI: 0.27, 0.85) for OS indicating a significant difference in OS favouring erlotinib plus CTX in a trial of 91 patients (Analysis 1.1).

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 can not be entered into a meta-analysis one of the SRs has a correction for this using an assumption JAG .

The median overall survival was reported for TOPICAL which was 10.4 months (95% CI 5.5, 15.1) for erlotinib (n=17) vs 3·7 months (0.3, 49.3) for placebo (n=11).

Secondary outcomes:

1. Progression free survival

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

The pooled treatment effect estimate for four trials (HR of 0.30 (95% CI: 0.24, 0.38, fixed effect, I^2=74%, 4 trials) favoured erlotinib (OPTIMAL; EURTAC; TORCH; ENSURE). As there was a substantial amount of heterogeneity, a sensitivity analysis was performed using the random effect model and results were similar to the main analysis (HR 0.31 (95% CI: 0.20, 0.50). CHEN reported a HR of 0.55 (95% CI: 0.21, 1.46) for PFS indicating no significant difference between the groups. FASTACT 2 reported a significant difference in PFS favouring erlotinib plus CTX (HR of 0.25 (95% CI: 0.16, 0.39) (Analysis 1.2)

The median progression free survival was reported for TOPICAL which was 4.8 months (1.6, 8.8) for erlotinib (n=17) and 2.9 months (0.3, 10.1) for placebo (n=11).

2. Tumour response

The pooled treatment effect estimate for five trials (OPTIMAL; TORCH; EURTAC; GTOWG; ENSURE) favoured erlotinib (RR 2.26 (95% CI: 1.85, 2.76, I^2=57%, 5 trials). As there was a substantial amount of heterogeneity a sensitivity analysis was performed using a random effect model and results were similar (RR 2.20 (95% CI: 1.53, 3.17), Analysis 1.3).

CHEN reported a RR of 0.83 (95% CI: 0.19, 3.67) for tumour response, indicating no significant differences in tumour response between the groups in a trial of 24 patients.

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

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

3. Toxicity and adverse effects of treatment b b

The most commonly reported AEs Table 1 in patients treated with erlotinib as a monotherapy (CHEN;ENSURE; EURTAC; GTOWG; OPTIMAL; TOPICAL; TORCH) were rash, diarrhoea and fatigue. Other AEs included mouth ulcers, constitutional symptoms nausea, increased ALT, dyspnoea and pulmonary toxicities. Where erlotinib was administered in combination with cytotoxic chemotherapy (FASTACT 2), the commonly reported AEs were neutropenia, thrombocytopenia and anorexia.

4. Quality of life

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

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

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

OPTIMAL used the FACT L, Lung cancer symptom score (LCSS) and trial outcome index (TOI) scales to assess QoL. The odds ratios (with co-variates EGFR mutation type, smoking history and histological type) were in favour of erlotinib and were 6.69 (95% CI: 3.01, 14.85; p=0.0001), 7.54 (95% CI: 3.38, 16.85; p= 0.0001), and 8.07 (95% CI: 3.57, 18.26; p=0.0001).

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 0.34-0.76 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 0.44-0.93 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 vs chemotherapy, and no major differences were observed. No statistical analyses were provided by the authors.

In the OPTIMAL trial, it was reported that the time to improvement of symptoms on Trial outcome index (TOI), LCSS and EORTC Q-30 was significantly shorter for erlotinib compared to chemotherapy FACT-L 1.51 vs 3.19 months (p=0.0067); TOI 2.79 vs 3.48 months (p=0.003); LCS 1.48 vs 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 respectively for FACT-L, TOI and LCS).

In the ENSURE trial, preliminary data has shown using the FACT-L questionnaire, that time to symptomatic progression was 13.8 months for erlotinib compared to 5.5 months for chemotherapy (HR 0.56 (0.36-0.87) p=0.0076.

Gefitinib vs CTX

Gefitinib vs gemcitabine plus cisplatin: One trial considered this comparison (First-SIGNAL).

Gefitinib vs paclitaxel plus carboplatin: Two trials considered this comparison (IPASS; NEJSG).

Gefitinib vs docetaxel plus cisplatin: One trial considered this comparison (WJTOG3405).

Data could not be combined for all four trials comparing gefitinib to CTX (First-SIGNAL; IPASS; NEJSG; WJTOG3405) as two trials only reported adjusted analyses (IPASS; NEJSG). It is not advisable to combine adjusted and unadjusted estimates.

Gefitinib and carboplatin plus paclitaxel or cisplatin plus gemcitabine vs CTX alone: Two trials considered this comparison (INTACT 1; INTACT 2). However, EGFR M+ specific data from both trials have been analysed as though they were one trial and therefore data are only presented narratively.

Gefitinib plus pemetrexed and cisplatin versus pemetrexed plus cisplatin. One trial considered this comparison (Yu 2014)

Primary outcome: Overall survival -

The pooled treatment effect estimate for two trials (IPASS; NEJSG) indicated no significant difference in OS between the groups (HR 0.95 (95% CI: 0.77, 1.18), I^2=0, 2 trials). First-SIGNAL reported a HR of 1.04 (95% CI: 0.50, 2.20) and WJTOG3405 reported a HR of 1.25, 95% CI 0.88-1.78 for OS indicating no significant difference in OS between the groups (Analysis 2.1).

INTACT 1 and INTACT 2 reported a combined HR of 1.77 [95% CI: 0.50, 6.23] for OS indicating no significant difference in OS between the groups.

Secondary outcomes:

1. Progression free survival

The pooled treatment effect estimate for two trials (IPASS; NEJSG) showed a significant difference in PFS between the groups favouring gefitinib (HR 0.39 (95% CI: 0.32, 0.48), I^2=73%, 2 trials). As there was a substantial amount of heterogeneity, a sensitivity analysis was performed using a random effect model and results were similar (HR 0.39 (95% CI: 0.26, 0.59)). First-SIGNAL reported a HR of 0.54 (95% CI: 0.27, 1.10) for PFS indicating no significant difference in PFS between the groups and WJTOG3405 reported a significant difference in PFS favouring gefitinib (HR 0.49 (95% CI: 0.34, 0.71), Analysis 2.2). ? no pooling ? adjustedcf unadjusted issue again

INTACT 1 and INTACT 2 reported a HR of 0.55 [95% CI: 0.19, 1.60] for PFS indicating no significant difference in PFS between the groups in a combined total of 32 patients.

2. Tumour response

The pooled treatment effect estimate for four trials (First-SIGNAL; IPASS; NEJSG; WJTOG3405) favoured gefitinib (RR 1.87 (95% CI: 1.60, 2.19, I^2=58%, 4 trials), Analysis 2.3). As there was a substantial amount of heterogeneity a sensitivity analysis was performed using a random effect model and results were similar (RR 1.92 (95% CI: 1.46, 2.52)).

Response at crossover after progression on first-line treatment

NEJSG report 28.2% of 52 patients in the NEJSG trial responded to carboplatin/paclitaxel after progressing on gefitinib, and 58.5% of 106 patients responded to gefitinib after failing carboplatin and paclitaxel.

INTACT 1 and INTACT 2 reported that 72% (13/18) of EGFR M+ patients responded to gefitinib plus CTX while 40% of EGFR M+ patients (2/5) responded to CTX alone.

3. Toxicity and adverse effects of treatment

For gefitinib monotherapy (First-SIGNAL; IPASS; NEJSG; WJTOG3405), the most commonly reported AE Table 1 was rash, followed by liver toxicity, anorexia and diarrhoea. For patients treated with gefitinib plus cytotoxic chemotherapy, (INTACT 1; INTACT 2) the commonly reported AEs were thrombocytopenia, rash, diarrheoa and neutropenia.

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 (WJTOG3405;INTACT 1) and not available for the EGFR M+ subgroup in one trial (First-SIGNAL).

IPASS used the FACT-L and TOI symptom improvement by the lung cancer subscale (LCS), and achieved 89.5% compliance for CTX and 94.8% for the gefitinib patients. The proportion of patients showing improvement in FACT-L total score, TOI and LCS significantly favoured gefitinib over carboplatin plus paclitaxel (FACT-L total score 70.2% vs 44.5%; odds ratio (OR) 3.01 (95% CI: 1.79, 5.07), TOI 70.2% vs 38.3% OR 3.96 (95% CI: 2.33, 6.71), LCS 75.6% v 53.9%, OR 2.70 (95% CI: 1.58, 4.62)). The time to deterioration data showed a median of 15.6 months for gefitinib compared to 3.0 months for CTX for FACT-L, 16.6 months compared to 2.9 months for TOI and 11.3 months compared to 2.9 months for LCS respectively. In the 131 patients who improved on the gefitinib arm, 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 patients (63%) on chemotherapy and 76 patients (69%) on gefitinib. They used three categories of physical, mental and 'life' wellbeing, each of which had three sub-categories. The number of patients improved/ stable/ worse is also reported and there was no difference between the treatment arms in mental wellbeing. However, the physical and life scales were all better for gefitinib than CTX. The data for daily functioning is quoted as HR 0.32 (95% CI: 0.17, 0.59; p.0001).

5. Symptom palliation

In the NEJSG trial, patients who received gefitinib had a significantly longer time to deterioration up to 20 weeks than patients 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, 0.46; p=0.0001) in favour of gefitinib.

Afatinib vs CTX

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

Afatinib vs 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 1.01 (95% CI: 0.78, 1.31), I^2=0, n=2 trials, Analysis 3.1), although data for LUX-Lung 6 are immature.

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, 0.53), I^2=90%, n=2 trials, Analysis 3.2). As there was a substantial amount of heterogeneity, a sensitivity analysis was performed using a random effect model and results were similar (HR 0.41 (95% CI: 0.20, 0.83).

2. Tumour response

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

3. Toxicity and adverse effects of treatment

The most commonly reported AEs in the afatinib-treated patients (LUX-Lung 3; LUX-Lung 6) were rash and diarrhoea, paronychia and stomatitis/mucositis Table 1.

4. Quality of life

LUX-Lung 3, using the QOL C-30 scale, improvement was noted in global health, overall health, physical, cognitive and role function in favour of afatinib over cisplatin plus pemetrexed chemotherapy.

LUX-Lung 6 also used the QOL C-30 scale and the lung cancer specific module QLQ-LC13 with >90% compliance. In the LUX-Lung 6 trial the EORTC QLQ-C30 and the lung cancer specific module QLQ-LC13 were used and showed that compared to cisplatin/gemcitabine a greater percentage of patients showed improvement in global health scores/QoL scores (p<0.0001, physical (p<0.0001) and social function (p<0.0001) with afatinib. 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, 0.87) p=0.007 and HR 0.68 (95% CI: 0.50, 0.93 p=0.02) respectively. The HR for pain 0.83 (95% CI: 0.62, 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 (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, 0.77, p=0.0002).

Cetuximab plus CTX vs CTX

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

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

Primary outcome: Overall survival

Data could not be pooled for the two trials comparing cetuximab plus CTX to CTX as one trial only reported an adjusted analysis (FLEX).

BMSO99 reported a HR of 1.62 (95% CI: 0.54, 4.84) for OS indicating no significant difference in OS between the groups (

Analysis 4.1).

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

Secondary outcomes:1. Progression free survival

Data could not be pooled for the two trials comparing cetuximab plus CTX to CTX as one trial only reported an adjusted analysis (FLEX).

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

FLEX reported a HR of 0.92 (95% CI: 0.53, 1.60) for PFS 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, 2.47, I^2=40%), n=2 trials) indicated no significant difference between the groups (Analysis 4.3).

3. Toxicity and adverse effects of treatment

The most commonly reported AEs Table 1 in the cetuximab-treated patients (BMSO99; FLEX) were neutropenia, leukopenia, febrile neutropenia and fatigue. It should be noted that cetuximab was administered in addition to cytotoxic chemotherapy and not as a monotherapy.

4. Quality of life

The cetuximab plus CTX trial (FLEX) used QOL C-30 and the LCSS and found no difference compared to CTX alone across all entered patients.

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 adverse events (AEs) differed across the 19 included trials. In Table 1 we describe 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 are for overall trial populations and therefore include non-EGFR M patients in trials where patients were unselected. In Table 1 the trials are grouped according to the EGFR-targeted treatment employed (afatinib, erlotinib,gefitinib,cetuximab).

Pneumonia is often associated with lung cancer and can be difficult to distinguish from pneumonitis, a recognised adverse effect of the TKIs. The authors did not consider these reports as reliable, and have quoted a large meta-analysis of data from separate groups of patients treated with erlotinib and gefitinib in the Discussion. LUX lung 3 and LUX lung 6 reported 3 and 2 patients with interstitial lung disease respectively (1%) in the afatinib arms.

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

Assessment of reporting biases

Sufficient trials were not included in the meta-analyses in order to construct a funnel plot to assess publication bias. However, we devised and carried out a thorough search strategy to reduce the impact of publication bias.

Subgroup analyses

Sufficient trials were not included to allow subgroup analyses.

Sensitivity analyses

We were unable to include sufficient trials in any one meta-analysis that would allow the sensitivity analyses specified in the methods section to be undertaken. However, where we detected moderate heterogeneity we used a random effect model as a sensitivity analysis to compare results with the fixed effect model. These are reported in the effect of interventions section.

Network meta-analysis

We considered that network meta-analysis (NMA) was not appropriate due to the different populations aross the included trials. We identified other barriers to conducting NMA: two trials reported adjusted analyses (IPASS; NEJSG) whereas all other trials reported unadjusted analyses; patients 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. 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.

Summary of findings table

Summary of findings ables are presented for pooled analyses for the outcomes of OS and PFS.

Discussion

Summary of main results

This review includes 19 RCTs with a combined total of 2317 patients with EGFR M+ NSCLC. We identified four EGFR-targeted treatments: afatinib (2 trials); erlotinib (8 trials); gefitinib (6 trials); cetuximab (2 trials). We did not consider that NMA would be appropriate due to the different populations of included trials, the reporting of adjusted analyses vs unadjusted analyses and the inappropriate use of the Cox proportional hazards model in some trials.

Our primary endpoint was OS for which we found no evidence of any robust OS benefit for any of the EGFR-targeted treatments when compared with CTX or placebo. The findings of one trial (FASTACT 2) did report a statistically significant OS gain for patients treated with erlotinib plus CTX when compared to CTX alone; however, this was based on a small sample of 97 patients. The trial employed an intercalated approach to avoid potential antagonism from concomitant chemotherapy and TKI. The majority of the included trials of monotherapy allowed patients to switch treatments on disease progression and this will have a confounding effect on any OS analysis. No OS effect was demonstrated in exploratory analyses of erlotinib in OPTIMAL or EURTAC or gefitinib IPASS, WJTOG3405 or NEJSG. A recent paper reports a pre-specified analysis of the Del19 subgroup across a pooled analysis of both of the afatinib trials. The analysis demonstrates an OS advantage for afatinib compared to chemotherapy, while the L858R subgroup (codon 21 mutation) showed no OS benefit (Yang 2014). Notably, crossover to afatinib in the control arm was not available, whilst in the majority of comparisons of erlotinib and efitinib with CTX, crossover to the corresponding TKI was allowed.

For the secondary endpoint of PFS, a pooled analysis of 4 trials of erlotinib (ENSURE; EURTAC; OPTIMAL; TORCH) demonstrated a statistically significant benefit compared with CTX (HR=0.31; 95% CI: 0.24 to 0.39) in 595 patients. Of the non-pooled trials, for erlotinib vs CTX, CHEN reported a non-significant 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). In a pooled analysis of gefitinib trials (n= 491) IPASS and NEJSG 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 2 trials that featured gefitinib (INTACT 1; INTACT 2) reported no difference between a regimen of gefitinib plus CTX compared with CTX plus placebo (n=32). Heterogeneity was high in the pooled analyses of both erlotinib and gefitinib. Five trials (LUX-Lung 3,EURTAC, OPTIMAL,NEJSG,IPASS) all showed a significant improvement in PFS for the TKI in tumours harbouring the Del19 mutation compared to chemotherapy. Meta-analysis of this mutation site -specific data has not been performed.

In a pooled analysis of afatinib (N=709) LUX-Lung 3; LUX-Lung 6 a statistically significant PFS benefit in favour of afatinib compared with chemotherapy was found (HR=0.42; 95% CI 0.34 to 0.53). It should be noted that the LUX-Lung 3 trial used cisplatin plus pemetrexed as the comparator, a chemotherapy combination demonstrated to have a superior OS benefit compared with cisplatin plus gemcitabine in non-squamous NSCLC (Brown 2013). No statistically significant PFS benefit for cetuximab plus CTX (n=81) was reported in either of the two trials (BMSO99; FLEX). It is not possible to draw any conclusions as to the advantages of adding CTX to targeted therapy from these data.

In the analysis of tumour response, a pooled analysis of 4 trials of erlotinib including 387 patients (EURTAC; GTOWG; OPTIMAL; TORCH) favoured treatment with erlotinib (RR=2.57; 95% CI:1.97 to 3.34). One single trial of erlotinib plus CTX (n=97) also favoured treatment with erlotnib (FASTACT 2) whilst 1 other small trial of erlotinib vs CTX (CHEN) reported no benefit of erlotinib (n=24, respectively). For gefitinib, all 6 trials demonstrated a statistically significant benefit for gefitinib compared to CTX; a pooled analysis of 4 trials including 648 patients (First-SIGNAL; IPASS; NEJSG; WJTOG3405) yielded a RR of 1.87 (95% CI:1.60 to 2.19). Both afatinib trials (n=709) reported a statistically significant benefit of afatinib compared with CTX (LUX-Lung 3; LUX-Lung 6) and the pooled analysis yielded an 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 AEs for patients treated with TKI monotherapy were rash, diarrhoea, paronychia, stomatitis/mucositis (afatinib), rash, diarrhoea and fatigue (erlotinib and gefitinib). These 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. Patients treated with cytotoxic CTX experienced the AEs usually associated with this treatment, e.g. neutropenia, febrile neutropenia, leukopenia and fatigue. It is however, difficult to accurately characterise and compare AEs across trials due 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 (Shi 2014) of erlotinib and gefitinib trials reported an incidence of 1.2% for interstitial lung disease with a mortality rate of 22.8%. The data presented for afatinib suggests this rare but serious complication occurs as frequently with all three TKIs, although no data on duration of therapy was provided. In addition, it should be cautioned 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 CTX (Pilkington 2012).

Quality of life for patients with EGFR M+ tumours was measured by a number of different methods in six trials (2 comparing afatinib with CTX, 2 comparing erlotinib with CTX and 2 comparing gefitinib with CTX) and a beneficial effect of the TKI compared to CTX was reported in all six trials. Symptom palliation of cough, pain and dyspnoea was shown for all three TKIs although there was no standardisation of methodology used.

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 3-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 9-12 months. In the 2 gefitinib trials where data were presented, the number of patients discontinuing therapy was similar to that for CTX, while in the

EURTAC trial a higher proportion of patients on chemotherapy than erlotinib discontinued on account of toxicity.

Overall completeness and applicability of evidence

The number of events remains small and the analyses remain preliminary in many trials (author calculated median follow-up of 28 months). We expect mature data in the next 2 years. Median survival of patients with advanced Stages III, IV NSCLC is of the order of 12 months, and of adenocarcinomas 18 months. At present, there is no indication that increases in PFS fully translate into OS benefit. This is consistent with the evidence in the current literature base (Booth 2012). However, there is wide variation in the selection criteria for these different trials, including age, sex, smoking and EGFR sequencing method based criteria. The later trials recruited patients only with proven EGFR mutations and longer survival times are seen. However, with the comparatively short survival in NSCLC, AEs and QoL for either first-line or second-line treatments are important. The interpretation of OS is limited by crossover in most trials. From the limited data available on crossover 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). 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 where a tissue biopsy is sampled 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 et al 2013). Secondly, methodological issues in the assessment of EGFR mutations may contribute to false negative results (Vogelstein 2013). Immunohistochemical-only categorisation of mutation was excluded from this review.

There are limited data provided on the types of mutations in relation to their sensitivity to targeted therapy (EURTAC). Of the three common sites of mutation, there is some evidence that tumours with codon 20 mutations are more resistant than exon 19 or L858R codon 21 mutations (Yasuda 2011). A preliminary report of a pooled analysis of patients with an exon 19 deletions or L858R mutations showed improved survival of afatinib compared to CTX (HR 0.81 CI 0.66-0.99 p<0.037) (Yang 2014). Some trials did not include assessment of exons 18 and 20 mutations. Secondly K-RAS and HER-2 mutations may be associated with resistance to primary treatment (Linardou 2008), but in the cetuximab trials they were assessed and demonstrated no predictive effect of the biomarkers. Non-randomised trials have shown that some mutations, principally T90M in codon 20, may contribute to the development of acquired resistance to these agents (Kosaka 2006; Rosell 2011; Su 2012). Only two of the included trials excluded T90M mutations (NEJSG;FLEX).

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 (e.g. from CTX) at an earlier or later stage of NSCLC management. This review provides strong data supporting first-line EGFR TKI in patients where EGFR mutation status is known to be positive. As mutation testing is not universally available, or the response time of reporting is prolonged, chemotherapy may be an acceptable first-line option where 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 patients in 50 phase II and III trials (Hasegawa 2011). It is less well established if there are ethnic differences in response to targeted therapies and the trials reported showed wide variation in the ethnic composition of the trials and the majority of the data comes from Asian patients.

Quality of the evidence

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

The Risk of Bias table (Figure 2; Figure 3) indicates a mixed risk of bias across the included trials for the majority of the assessment criteria, most trials are at an unclear or high risk of bias. The two items that were considered to be at high risk of bias across the trials were related to blinding of treatment allocation for patients and personnel and blinding of outcome assessment. In trials that compare oral therapy with intravenous chemotherapy treatments, blinding of participants and administrators is difficult to achieve and even if blinding procedures were implemented, the appearance of a rash (a common side-effect of treatment with a TKI) would indicate the treatment regime 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, for erlotinib OPTIMAL did not report blinding of outcome assessment, neither did IPASS or WJTOG3405 for gefitinib. We acknowledge that some trials may have implemented such procedures but did not report on them.

The comparisons with CTX were in general direct, but there was wide variation in the choice of CTX in the comparator arm. This reflects variation in clinical practice and in particular performance status and co-morbidity 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 used doublet chemotherapy combinations utilised in the other trials, and patients for both these trials were selected on the basis of age (>70) and not primarily performance status. The trials also varied in the extent to which they included never or former smokers, and in the male/female ratio. The other major factor contributing to heterogeneity is ethnicity, as the 8 trials recruiting exclusively in Asia contributed 64% of the patients. All these factors may contribute to variation in drug handling of both CTX and targeted therapy. Heterogeneity was high for

assessment of PFS for erlotinib, gefitinib and afatinib comparisons in the pooled data.

A degree of caution should be taken in the interpretation of the results. Only 7 of the included trials recruited patients solely based on their EGFR mutation status (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. It is worth noting however, that the subgroup of EGFR M+ patients in the IPASS trial, at 261, was larger than the the total trial population of four of the EGFR M+ only trials (EURTAC; NEJSG; OPTIMAL; WJTOG3405). It should be further noted that for 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). These four trials however provided data from only 113 patients, and 80 of these were participants in the cetuximab trials. We do not believe this factor has an impact on the conclusions in respect of the three TKIs.

The confidence limits of the PFS and OS plots are narrow, with the exception of the small trial with erlotinib (CHEN) and suggest the data are precise. Wider confidence limits are seen for response, which may reflect the subjective nature of the assessment, even with external review, and current concerns PFS is the better end-point for trial assessment where crossover is a factor (Booth 2012).

There is evidence that Asian patients have a different proportion of EGFR M+ and differing relationship to smoking which may imply these are biologically different diseases. Of the 2317 patients reported on in this review, 1591 were recruited exclusively in trials conducted in Asian countries. We can find no evidence there is a different set of mutations in Asian and Caucasian 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 patients. 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 patients 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 patients given TKIs in first-line, second-line and maintenance RCTs also supported gain in progression-free survival in EGFR M+ patients treated with erlotinib and gefitinib (Lee 2013). This analysis included data on subgroups of patients (n= 67) from TALENT, TRIBUTE and TOPICAL which were not available to us at the time of analysis. No data on patient characteristics, toxicity and quality of life were analysed in the Lee review. 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 CI 0.38-0.49 ($p<0.001$) for PFS and no effect on OS. As described above, we consider this pooling 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 7 Hasegawa 2015 and 8 phase III trials 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. Our review of patients across 19 trials includes additional trials and comparable data from the 2317 EGFR M+ patients on afatinib, erlotinib and gefitinib. A recent individual patient meta analysis (Pujol 2014) of four RCTs of cetuximab (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 ? Add necitumumab .

Authors' conclusions

Implications for practice

Erlotinib, gefitinib and afatinib are effective 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 based on both these criteria, although only 6 trials reported on quality of life solely in the EGFR M+ population. The majority of trials included patients with a PS of 1 and 2, but the data on AEs suggest some PS 3 as well as elderly patients might tolerate the agents better than cytotoxic CTX (GTOWG;CHEN). They may also be an alternative to best supportive care in patients unsuitable for chemotherapy. Other reviews (Brown 2013) have concluded that the CTX standard for non-squamous NSCLC should now be cisplatin and pemetrexed, at least in patients of good PS. In locations where mutation testing is not available a decision may have to be made on the basis of histology, gender, smoking history and ethnicity about the selection of first-line TKI therapy or chemotherapy. In patients with good PS, the intercalated regimen of erlotinib and CTX is another option for this population in view of its OS benefit in one trial (FASTACT 2). Mature data on OS expected within 2 years should provide more definitive guidance.

The AEs summarised in this review have underlined the difference between the reduced toxicities experienced with TKI therapy and those associated with cytotoxic chemotherapy. This will have implications for care of patients and the costs of healthcare provision (Pilkington 2012).

Implications for research

Future trials of these agents should comprise patients with known EGFR mutations, and attempt to clarify the effectiveness in the individual mutant subtypes (codons 19,20 and 21) as well as the small numbers with multiple mutations and rare mutations. There is increasing evidence that patients with T90M mutations should be excluded from trials with afatinib,

erlotinib and gefitinib. Irreversible inhibitors of EGFR are under development along with monoclonal antibody therapies in addition to cetuximab. Biomarker trials may help to select patients in which optimal activity will be demonstrated - for example codon 19-21 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 patient with tumours harbouring the T90M mutation (Janne 2014). It follows that stratification of NSCLC patients by an appropriate molecular profile will progressively evolve 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; INTACT 2 trials do not favour this approach, either in terms of efficacy or toxicity. The FASTACT 2 trial demonstrated positive outcomes from the combination of erlotinib with CTX given in an intercalated design; however, the number of EGFR M+ patients in these trials was small. Three randomised trials have addressed the issue of maintenance therapy after a response or stable disease to CTX, two with erlotinib (Capuzzo 2010: Perol 2012), the third with gefitinib (Zhang 2012) see meta analysis review - can't find this now . These trials showed an overall PFS gain for maintenance erlotinib or gefitinib respectively, and this effect was significant in the EGFRM+ subgroups in the Capuzzo 2010 and Zhang 2012 trials. There was no significant OS benefit in any of the maintenance trials. These trials may be worth repeating with patients selected by EGFR M+ status. Crossover 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 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, and the focus should be on identifying the predictive value of specific mutations to optimise survival and minimise toxicity. Future trials should report in detail on the degree and duration of symptom control as well as quality of life scores.

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Contributions of authors

All review authors listed below contributed to the text or data section, or both, and analysis. All review authors took part in the editing and production of the review, including Fergus Macbeth, Ian Stubbin and Ivan Sola.

J A Green: input into all aspects of the review

VB: data extraction, entry and analysis

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

AB: project management

PJ: clinical review

FV: searching, data extraction, entry and analysis

KD: statistical advisor

YD: searching, trial screening

Declarations of interest

Pooja Jain has had sponsorship from Eli Lilly, Roche Ltd, Pierre Fabre and Boehringer Ingelheim to attend conferences. She has also attended advisory boards for Eli Lilly, Roche and Boehringer Ingelheim.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

BMSO99

Methods	Open-label, randomised, phase III, multicentre 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 patients 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. Patients with previously treated CNS metastases accepted, but patients 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 chimerized/murine MABs; pregnant/nursing women;history of acute myocardial infarction (3 months prior); Grade 2 peripheral neuropathy; inadequate hematologic, hepatic, or renal function. Median age: 64 years Male:57% Ethnicity: 88% White
Interventions	Treatment arm (8/338 patients EGFR M+): cetuximab plus taxane/carboplatin Comparator arm (9/338 patients EGFR M+): taxane/carboplatin 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 75mg/m^2, 1-hour IV) with carboplatin (area under the curve = 6, 30-minute IV) on day 1 every 3 weeks until disease progression or intolerable toxicity for six cycles.
Outcomes	Primary outcome: PFS (based on modified WHO criteria) Secondary outcomes: ORR, OS, QoL, safety
Mutation Assessment Method	QiAamp
Exons assessed	18-21
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 end point). Ten 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 end point of PFS. Patient accrual was increased from 300 to 660 patients.

Risk of bias table

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)	High risk	This was an open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Independent radiological assessment was undertaken.
Incomplete outcome data (attrition bias)	Low risk	13 patients in cetuximab arm did not receive treatment; 18 patients 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 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 0–3; measurable lesion(s); no previous radiotherapy on measurable lesion(s); adequate bone marrow reserve with a granulocyte count more than or equal to 1500/mm3, platelets more than or equal to 100,000/ mm3, 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% E.Asian
Interventions	Treatment arm (9/57 patients EGFR M+): erlotinib 150 mg/daily Comparator arm (15/56 patients EGFR M+): vinorelbine 60 mg/m^2 days 1 and 8 of every 3-weekly cycle Responding patients and those with stable disease continued treatment until disease progression or completion of six cycles. Patients could continue treatment beyond six 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	18-21
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 table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states that patients were randomised with stratification. No other information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given.
Blinding of participants and personnel (performance bias)	High risk	The trial was open-label.
Blinding of outcome assessment (detection bias)	High risk	No evidence of independent assessment of PFS.
Incomplete outcome data (attrition bias)	Low risk	All patients were accounted for.
Selective reporting (reporting bias)	Unclear risk	The protocol states that Time to Progression is a primary 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 (CTX)
Participants	217 patients 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 i.v. days 1 and 8 plus cisplatin 75 mg/m^2 i.v. day 1, every 3 weeks, for up to four 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 cut-off July 2012 and OS data cut-off April 2014

Risk of bias table

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)	High risk	The trial was open label
Blinding of outcome assessment (detection bias)	Low risk	Independent radiological assessment used as a sensitivity analysis
Incomplete outcome data (attrition bias)	Low risk	All patients 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 (CTX)
Participants	173 patients with NSCLC and EGFR mutations. Inclusion Criteria:Histological diagnosis of Stage IIIB (with pleural effusion) or Stage IV NSCLC (based on the sixth 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 (neo adjuvant 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 patients EGFR M+): erlotinib 150 mg/daily until disease progression, toxicity or withdrawal of consent Comparator arm (87/87 patients EGFR M+): cisplatin 75 mg/m² on day 1, docetaxel 75 mg/m² on day 1 or gemcitabine 1250 mg/m² on day 1 and 8. Cycle of 3 weeks for up to 4 cycles Patients who were ineligible for cisplatin treatment received intra venous carboplatin chemotherapy instead (3 week cycles of AUC 6 on day 1 with 75 mg/m² docetaxel on day 1, or AUC 5 on day 1 with 1000 mg/m² gemcitabine on days 1 and 8).
Outcomes	Primary Outcome: PFS (RECIST version 1 criteria) Secondary Outcomes: OS, ORR
Mutation Assessment Method	ABI Prism 3130 DNA Analyzer
Exons assessed	19, 21
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled patients were EGFR positive. Trial enrolment was stopped at interim data analysis as trial had met primary endpoint

Risk of bias table

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)	High risk	The trial was open-label.
Blinding of outcome assessment (detection bias)	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)	Low risk	All patients 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): E=28; CTX=28 The trial included a mixed patient population. The analysis of EGFR M+ data only (n= 97) is presented as subgroup analysis in the primary published paper.
Participants	451 patients with stage IIIB/IV NSCLC. Inclusion criteria: ECOG PS 0 or 1; measurable disease according 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; and localised radiotherapy; brain metastasis; any unstable illness; patients known to be HIV positive Median age: 58 years Male:60% Ethnicity: 100% SE Asian
Interventions	Treatment arm (49/226 patients EGFR M+): erlotinib 150mg per day plus gemcitabine (1250 mg/m² on days 1 and 8 of a 4 week cycle, intravenously) plus platinum (carboplatin 5 × AUC or cisplatin 75 mg/m² on day 1 of a 4 week cycle) Comparator arm (48/225 patients EGFR M+): placebo plus gemcitabine (1250 mg/m² on days 1 and 8 of a 4 week cycle, intravenously) plus platinum (carboplatin 5 × AUC or cisplatin 75 mg/m² on day 1 of a 4 week cycle) plus placebo
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 table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients 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)	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)	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)	Low risk	All patients 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 an presented in published paper
Other bias	Unclear risk	Trial sponsored in part by pharmaceutical company.

First-SIGNAL

Methods	Open-label, randomised, multi-centre 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 subgroup analysis in the primary published paper.
Participants	313 Korean never-smokers patients with Stage IIIB or IV lung adenocarcinoma. Inclusion Criteria: chemotherapy-naive never-smokers older than age 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 Median age: 57 years Male:11% Ethnicity: 100% E Asian
Interventions	Treatment arm (26/159 patients): gefitinib 250 mg/daily until disease progression Comparator arm (16/154 patients): cisplatin 75 mg/m^2 on day 1 and gemcitabine 1,250mg/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 table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients 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)	High risk	The trial is open-label.
Blinding of outcome assessment (detection bias)	Low risk	Independent blinded assessment of PFS is reported
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for (4 withdrew consent in gemcitabine arm prior to treatment).
Selective reporting (reporting bias)	Low risk	No protocol available but all outcomes stated as measured in paper 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; CTX = 24 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 one positively stained tumour cell. Inclusion criteria: >18 years, ECOG PS 0-2, adequate organ function, at least one 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 patients EGFR M+): cetuximab plus cisplatin and vinorelbine. Cetuximab starting dose of 400 mg/m² intravenous infusion over 2 hrs on day 1, and from day 8 onwards at 250 mg/m² over 1 hr per week. Cisplatin 80 mg/m² intravenous infusion on day 1, and vinorelbine 25 mg/m² intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles. Comparator arm (36/568 patients 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 EGFR29 Mutation Test Kit
Exons assessed	19
Notes	

Risk of bias table

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)	High risk	Open-label.
Blinding of outcome assessment (detection bias)	High risk	Open-label. No evidence of independent assessment of radiological outcomes
Incomplete outcome data (attrition bias)	Low risk	All patients 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 patients with EGFR M+ tumours (n=10) is retrospective in the primary publication.
Participants	284 patients aged 70 years or older with Stage IIIB or IV NSCLC.
Interventions	Treatment arm (144 patients): erlotinib 150mg/daily Comparator arm (140 patients): carboplatin AUC 5 d1 and vinorelbine 25mg/m^2 day 1, 8 every 21 days for up to 6 cycles
Outcomes	Primary outcome: PFS (RECIST criteria) Secondary outcomes: OS, response, tolerability, quality of life
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 analyser. Quality of life is not reported, nor is OS or PFS for EGFR M+ pts. Trial Information taken from poster provided by trial authors.

Risk of bias table

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)	Unclear risk	No information. No information provided. Trial information taken from conference abstract
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	Unclear risk	Nine patients did not receive treatment but reasons not reported.
Selective reporting (reporting bias)	High risk	Quality of life not reported
Other bias	Unclear risk	Pharmaceutical company support not clear

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 patients (combined total of 32) is reported in a publication separate to the main trial publication.
Participants	1093 patients 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 localized 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 breast-feeding; 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 patients): gefitinib 500mg/daily plus gemcitabine 1,250 mg/m^2 IV 30 minutes on days 1 and 8 and cisplatin 80 mg/m2 after gemcitabine administration on day 1 only. Treatment arm B (365 patients): gefitinib 250mg/daily plus gemcitabine and cisplatin Comparator arm (363 patients): Placebo plus gemcitabine and cisplatin Chemotherapy was administered in 3-week cycles for a total of six cycles: Subsequently, patients continued on gefitinib or placebo until disease progression.
Outcomes	Primary outcome: OS Secondary outcomes: TTP (RECIST) , response rate and safety
Mutation Assessment Method	Big dye terminator
Exons assessed	18 to 21
Notes	Number of EGFR M+ patients unclear

Risk of bias table

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)	Low risk	Double blind placebo controlled design.
Blinding of outcome assessment (detection bias)	Low risk	No independent review but outcome assessors were blind.
Incomplete outcome data (attrition bias)	Unclear risk	No information.
Selective reporting (reporting bias)	Low risk	No protocol available but all outcomes stated as measured in paper 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 patients (combined total of 32) is reported in a publication separate to the main trial publication.
Participants	1037 patients 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 breast-feeding, and hypersensitivity to mannitol, corticosteroids, H2-antagonists, antihistamines, or agents formulated with polyoxyethylated castor oil Median age: 62 years Male:59% Ethnicity: 90% White
Interventions	Treatment arm A (347 patients): gefitinib 500mg/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 patients): gefitinib 250mg/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 patients): 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 six cycles in the absence of disease progression. Thereafter, patients 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	Big dye terminator
Exons assessed	18 to 21
Notes	Number of EGFR M+ patients unclear

Risk of bias table

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)	Low risk	Double blind placebo controlled design.
Blinding of outcome assessment (detection bias)	Low risk	No independent review. But outcome assessors were blinded
Incomplete outcome data (attrition bias)	Unclear risk	No information.
Selective reporting (reporting bias)	Low risk	No protocol available but all outcomes stated as measured in paper 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 patients who had advanced pulmonary adenocarcinoma and who were nonsmokers 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 nonsmokers (patients 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 had had no previous chemotherapy or biologic or immunologic therapy. Median age: 57 years Male:20% Ethnicity: 99% E Asian
Interventions	Treatment arm (132/609 patients EGFR M+): gefitinib 250 mg/daily Comparator arm (129/608 patients 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 LCS score), Safety, and adverse-event profile
Mutation Assessment Method	DxS EGFR29 mutation test kit
Exons assessed	18 to 21
Notes	

Risk of bias table

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 system was used (source Astra Zeneca evidence submission to NICE).
Blinding of participants and personnel (performance bias)	High risk	Open-label.
Blinding of outcome assessment (detection bias)	High risk	PFS was assessed according to RECIST criteria. However, no independent verification of assessments was reported.
Incomplete outcome data (attrition bias)	Low risk	All patients 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, phase III, international trial Length of follow-up (months): 16.4
Participants	345 patients 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% E Asian
Interventions	Treatment arm (345/345 patients EGFR M+): afatinib 40mg/day, escalated to 50mg if limited adverse events observed in cycle 1 until progression Comparator arm (115/115 patients EGFR M+): cisplatin 75mg/m^2 and pemetrexed every 21 days for up to 6 cycles
Outcomes	Primary Outcome: PFS Secondary Outcome: OS, ORR, Disease Control Rate, tumour shrinkage, QoL (EORTC QLQ C30 and LC 13), AEs
Mutation Assessment Method	Therascreen EGFR29
Exons assessed	18 to 21
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	BI'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.
Blinding of participants and personnel (performance bias)	High risk	Open-label trial.
Blinding of outcome assessment (detection bias)	Low risk	Open-label trial but with independent review.
Incomplete outcome data (attrition bias)	Low risk	All patients 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 Phase III randomised 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 mutation-positive at the screening stage. Median age: 58 years Male:34.% Ethnicity: 90% Chinese
Interventions	Treatment arm (242/242 patients EGFR M+) afatinib 40mg/day Comparator arm (122/122 pateints EGFR M+) gemcitabine 1000mg/m2 d 1 and 8 and cisplatin 75mg/m2 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 EGFR29
Exons assessed	19 to 21
Notes	HR 0.26 p<0.0001in favour of afatinib . Patient reported outcomes pain , cough and dyspnea all significantly improved

Risk of bias table

Bias	Authors' judgement	Support for judgement
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)	High risk	Open-label trial.Clinicians and patients were not masked to treatment assignment,
Blinding of outcome assessment (detection bias)	Low risk	The trial investigators who did assessments of patient-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)	Low risk	All patients 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 patients with metastatic, non–small cell lung cancer and EGFR mutations Inclusion Criteria: NSCLC with EGFR mutations, chemo-naive patients 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 patients EGFR M+): gefitinib 250 mg/daily until disease progression, toxicity or withdrawal of consent. Comparator arm (114/114 patients EGFR M+): carboplatin, dose equivalent to an area under the concentration–time curve[AUC] of 6, given intravenously over a 1-hour period on day one every 3 weeks and paclitaxel 200 mg per 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
Mutation Assessment Method	PNA-LNA
Exons assessed	19 to 21 (Excluding T90M)
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled patients were EGFR positive

Risk of bias table

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)	High risk	The trial was open-label.
Blinding of outcome assessment (detection bias)	Low risk	Independent radiological review conducted
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	None identified

OPTIMAL

Methods	Open-label, randomised, phase III multicentre trial conducted in China Length of follow-up (months): not reported
Participants	165 patients with NSCLC Inclusion Criteria: Confirmed EGFR mutations in exon 19 or exon 21 more than 18 years of age and 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
Interventions	Treatment arm (83/83 patients EGFR M+): erlotinib 150 mg/daily until disease progression Comparator arm (82/82 patients EGFR M+): carboplatin (area under the curve=5) on day 1 of a 3 weeks cycle and gemcitabine 1000 mg/m² 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 the Lung Cancer Subscale)
Mutation Assessment Method	Direct
Exons assessed	19 to 21
Notes	EGFR mutation analysis defined as inclusion criteria, therefore all enrolled patients were EGFR M+

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients 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)	High risk	Open-label
Blinding of outcome assessment (detection bias)	High risk	No independent review of radiological outcomes
Incomplete outcome data (attrition bias)	Low risk	All patients 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, phase III multicentre 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.
Participants	670 patients with newly diagnosed, pathologically confi rmed 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 confi rmed NSCLC; stage IIIb or IV disease; chemotherapy naive; no symptomaticbrain metastases; deemed unsuitable for chemotherapy because of poor ECOG PS (≥2) or presence ofseveral comorbidities (including impaired renal functionwith creatinine clearance <60 mL/min), or both;estimated life expectancy of at least 8 weeks;older than 18 years, diagnosis 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 patients EGFR M+): erlotinib 150mg/daily Comparator arm (11/320 patients 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 benefit sof erlotinib in a population of patients with NSCLC who were considered unsuitable for chemotherapy

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients 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 theCancer Research UK and University College London Cancer Trials Centre. All investigators, clinicians, and patients were masked to assignment.
Blinding of participants and personnel (performance bias)	Low risk	All investigators, clinicians, and patients were masked to assignment. Use of placebo.
Blinding of outcome assessment (detection bias)	Low risk	All investigators, clinicians, and patients were masked to assignment.
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for. ITT analysis conducted.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.
Other bias	Unclear risk	Risk of patients 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 patients with NSCLC Inclusion Criteria: histologically or cytologically confirmed NSCLC Stage IIIB (with malignant pleural effusion or supraclavicular nodes) or IV, at least one target or non-target lesion age younger than 70 years (no age limits for Canadian centres), ECOG PS 0 to 1. Patients 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. Patients with inflammatory eye surface changes and those who could not take or absorb oral medications. Median age: 62.5 years Male:66.% Ethnicity: 96% Caucasian
Interventions	Treatment arm (19/380 patients EGFR M+): erlotinib 150 mg/daily until disease progression Comparator arm (20/380 patients EGFR M+): cisplatin 80 mg/m2 intravenously on day 1 and gemcitabine 1,200 mg/m2 intravenously per day on days 1 and 8 every 3 weeks until progression.
Outcomes	Primary Outcome: OS Secondary Outcomes: Total progression-free survival (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 patients who were not included in the previous two 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 patients who were not included in the previous two categories. ORR, defined as the number of patients with complete or partial response at any time divided by the total number of patients enrolled onto each arm. All based on RECIST criteria. Toxicity
Mutation Assessment Method	Direct
Exons assessed	19
Notes	Early trial termination due to the demonstration of the non-inferiority of the experimental arm. This was a two-stage trial with erlotinib given as first-line treatment and cisplatin plus gemcitabine as second-line treatment.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were centrally randomly assigned to the two treatment arms (1:1 ratio) through a centralized automated minimization procedure by using histology (adenocarcinoma v other), smoking status (never v ever smoker), sex, age (70 v70 years), centre, and PS (0 v 1) as strata.
Allocation concealment (selection bias)	Low risk	Centralised admin system used.
Blinding of participants and personnel (performance bias)	High risk	The trial was open-label.
Blinding of outcome assessment (detection bias)	High risk	No evidence of independent assessment.
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Unclear risk	Paper states that further secondary end points are not reported in this article and included quality of life, comparisons of resource use, and studies of exploratory biomarkers in tumor and blood samples.
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, phase III randomised multi-centre 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 non-small-cell lung cancer or postoperative recurrence harbouring EGFR mutations. (Five patients 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 0–1, measurable or non-measurable disease and adequate organ function. Exclusion Criteria: previous drug therapy that had targeted EGFR, history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80. Median age: 64 years Male:36.% Ethnicity: 100% Japanese
Interventions	Treatment arm (86/86 patients EGFR M+): gefitinib 250 mg/daily Comparator arm (86/86 patients EGFR M+): cisplatin 80 mg/m², IV over ¬90-min once every 3 week cycle and docetaxel 60 mg/m², 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 patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six 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 patients were EGFR M+

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated at the data centre to each treatment group 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)	High risk	Open-label
Blinding of outcome assessment (detection bias)	High risk	No independent verification of PFS.
Incomplete outcome data (attrition bias)	Low risk	All patients 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 Astra Zeneca. The trial group is non-profit making but receives unrestricted funding from several pharmaceutical companies

Yu 2014

Methods	Open label, Phase II, single centre 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 chemo-naive patients with advanced (stage IIB or IV) non-squamous NSCLC. ECOG 0 or 1. Mean age=55 % Male= 50% Ethnicity+ Chinese
Interventions	Treatment arm (13/58 patients EGFR M+): gefitinib 250mg days 3 to 16 +pemetrexed 500mg/m^2 with cisplatin 75mg/m^2 or carboplatin AUC=5 every 3 weeks up to 6 cycles Comparator arm (18/59 patients EGFR M+): pemetrexed 500mg/m^2 with cisplatin 75mg/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 amximum of 6 cycles

Risk of bias table

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)	High risk	Open label trial
Blinding of outcome assessment (detection bias)	High risk	No evidence of independent radiological assessment
Incomplete outcome data (attrition bias)	Unclear risk	All patients 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

Footnotes

AE: Adverse event

AFA: Afatinib

AUC: Area under the curve

CET: Cetuximab

CTX: Chemotherapy

DCR: Disease control rate

ECOG PS: Eastern Cooperative Oncology Group performance status

EGFR M+: Epidermal growth factor receptor mutation positive

ERL: Erlotinib

FACT-L: Functional Assessment of Cancer Therapy - Lung

FISH: Fluorescence In Situ Hybridisation

GEF: Gefitinib

HER:Human epidermal growth factor receptor

IHC: Immunohistochemistry

ITT: Intention to treat

IV: Intravenous

IVRS: Interactive voice response system

IWRS: Interactive web response system

MABs:Monoclonal antibody

NSCLC: Non-small cell lung cancer

ORR: Overall response rate

OS: Overall survival

PFS: Progression free survival

PS: performance status

QoL: Quality of life

RECIST: Response Evaluation on Solid Tumours

STA: Single technology appraisal

TTP: Time to progression

TTR:Time to treatment response

WHO: World Health Organisation

Characteristics of excluded studies

Boutsikou 2013

Reason for exclusion	only patients surviving at 1 year were tested for EGFR mutation status

Crino 2008

Reason for exclusion	EGFR expression tested only

ECOG 4508

Reason for exclusion	Insufficient robust EGFR M+ samples available in trial

FASTACT

Reason for exclusion	Data for the 7 EGFR patients not in usable format

Gatzemeier 2003

Reason for exclusion	EGFR expression tested only

Goss 2009

Reason for exclusion	EGFR expression tested only

Heigener 2014

Reason for exclusion	The number of EGFR M+ patients was considered too small for analysis

Hirsh 2011

Reason for exclusion	TKI used in both trial arms

Janne 2012

Reason for exclusion	TKI used in both trial arms

JO25567

Reason for exclusion	TKI used in both trial arms

Lilenbaum 2008

Reason for exclusion	EGFR expression tested only

Massuti 2014

Reason for exclusion	TKI used in both trial arms

NEJ005 2014

Reason for exclusion	TKI used in both trial arms

NEJ009

Reason for exclusion	TKI used in both trial arms

Rosell 2004

Reason for exclusion	EGFR expression tested only

Rosell 2008

Reason for exclusion	EGFR expression tested only

Thatcher 2014

Reason for exclusion	EGFR testing by IHC

White

Reason for exclusion	Due to small sample size, survival analyses were not determined for patients with EGFR mutations

Xie 2015

Reason for exclusion	TKI used in both trial arms

Yang 2015

Reason for exclusion	TKI used in both trial arms

Footnotes

Characteristics of studies awaiting classification

INSPIRE

Methods	Open-label, randomised, phase III, international trial
Participants	633 patients with previously untreated, stage IV, non-squamous NSCLC
Interventions	Treatment arm (315 patients): necitumumab+pemetrexed and cisplatin Comparator arm (318 patients):pemetrexed and cisplatin Patients received either cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 of a 3-week cycle for a maximum of six 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, phase III, international trial
Participants	1159 patients with histologically documented, unresectable, locally advanced, recurrent or metastatic (Stage IIIb/IV) NSCLC, age 18 years, ECOG PS of 0 or 1;
Interventions	Treatment arm (580 patients): erlotinib 150mg/daily plus cisplatin and gemcitabine Comparator arm (579 patients): placebo plus cisplatin and gemcitabine gemcitabine 1,250 mg/m2 on days 1 and 8 and cisplatin 80 mg/m2 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, phase III multicentre trial conducted in the USA
Participants	1079 patients with histologically documented Stage IIIB or Stage IV NSCLC; age18 years; and ECOG PS of 0 or 1.
Interventions	Treatment arm (539 patients): erlotinib 150mg/daily plus paclitaxel and carboplatin Comparator arm (540 patients): placebo plus paclitaxel and carboplatin Paclitaxel 200mg/m^2 and carboplatin AUC 6 every 3 weeks until disease progression
Outcomes	Primary outcome: OS Secondary outcomes: TTP, ORR, AEs
Notes	

Footnotes

Characteristics of ongoing studies

ARCHER

Study name	ARCHER
Methods	Open-label, Phase III RCT conducted in Asia
Participants	440 Stage IIIB/IV NSCLC with at least one activating EGFR mutation.
Interventions	Dacomitnib 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

Footnotes

Summary of findings tables

1 Summary of findings

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous, NSCLC

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 [control]	Corresponding risk [experimental]				
Overall survival	67 per 100	66 per 100 (58 to 73)	HR 0.95 (0.77 to 1.18)	489 (2 studies)	Moderate	For Asian patients
Progression-free survival	89 per 100	57 per 100 (50 to 65)	HR 0.39 (0.32 to 0.48)	485 (2 studies)	Moderate	For Asian patients

*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 relative risk (RR) of the intervention where RR = (1 - exp(HR x ln(1 - assumed risk))) / assumed risk
CI: Confidence interval; **RR:** Risk Ratio; 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.

Footnotes

2 Summary of findings

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous, NSCLC

Patient or population: EGFR M+ patients with NSCLC

Settings: Oncology

Intervention: erlotinib

Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk [control]	Corresponding risk [experimental]				
Overall survival	56 per 100	54 per 100 (46 to 63)	HR 0.95 (0.75, 1.22)	429 (3 studies)	Moderate	Limited QOL - no European patients
Progression-free survival	73 per 100	34 per 100 (28 to 40)	HR 0.31 (0.25, 0.39)	595 (4 studies)	Moderate	Limited QOL - no European patients

*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 relative risk (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.

Footnotes

3 Summary of findings

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous, NSCLC

Patient or population: EGFR M+ patients with NSCLC

Settings: Oncology

Intervention: afatinib

Comparison: CTX

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk [control]	Corresponding risk [experimental]				
Overall survival	46 per 100	44 per 100 (37 to 52)	HR 0.93 (0.74 to 1.17)	709 (2 studies)	High quality	For Asian patients
Progression-free survival	56 per 100	29 per 100 (15 to 50)	HR 0.41 (0.20 to 0.83)	709 (2 studies)	High quality	For Asian patients

*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 relative risk (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.

Footnotes

Additional tables

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 patients in either group and if there was a >=10% difference between the groups	EGFR only	Rash/acne: 16.2% (AFA) vs 0% (CTX)	Diarrhoea: 14.4% (AFA) vs 0% (CTX)	Paronychia: 11.4% (AFA) vs 0% (CTX)	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 patients in any treatment group	EGFR only	Rash/acne: 14.6% (AFA) vs 0% (CTX)	Diarrhoea: 5.4% (AFA) vs 0% (CTX)	Stomatitis/mucositis: 5.4% (AFA) vs 0% (CTX)	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 (CTX)	Diarrhoea: 29.8% (ERL) vs NR (CTX)	Mouth ulceration: 14% (ERL) vs NR (CTX)	Decreased appetite: 26.3% vs NR Diarrhoea: 12.3% vs NR Vomiting: 10.5% vs NR Anorexia: 10.5% vs NR
ENSURE	Grade ≥3 ≥5% in either arm	EGFR	Rash: 6.4% (ERL) vs 1% (CTX)	Neutropenia, Leukopenia Anaemia: All 0.9% (ERL) vs 25%, 14.4%, 12.5% respectively (CTX)		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	Rash: 13% (ERL) vs 0% (CTX)	Fatigue: 6% (ERL) vs 20% (CTX)	Diarrhoea: 5% (ERL) vs 0% (CTX)	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% (CTX)	Thrombocytopenia 14% (ERL) vs 14% (CTX)	Anaemia: 11% (ERL) vs 9% (CTX)	Neutropenia: 25% vs 29% Thrombocytopenia: 14% vs 14% Anaemia:9% vs 11%

GTOWG	Grade 3/4	Unselected population	Rash: 12% (ERL) vs 0% (CTX)	Diarrhoea: 6% (ERL) vs 2% (CTX)	Constitutional symptoms: 3% (ERL) vs 5% (CTX)	Neutropenia: 36% vs 0% Leukocytes: 33% vs 0% Hemoglobin: 11% vs 0.7%
OPTIMAL	Grade 3/4 CTC (V3) AEs occurred in 3% or more in either treatment group	EGFR	Increased ALT: 4% (ERL) vs 1% (CTX)	Skin rash: 2% (ERL) vs 0% (CTX)	Diarrhoea: 1% (ERL) vs 0% (CTX)	Neutropenia: 42% vs 0% Thrombocytopenia: 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% (CTX)	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% (CTX)	Pulmonary toxicity: 9% (ERL) vs 6% (CTX)	Fatigue: 8% (ERL) vs 12% (CTX)	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% (CTX)	Anorexia: 13.8% (GEF) vs 57.3% (CTX)	AST: 11.3% (GEF) vs 2% (CTX)	Anorexia:57.3% vs 13.9% Neuropenia: 54% vs 1.9% Fatigue: 45.3% vs 10.1%
INTACT1	Grade 3/4 CTC Commonly occurring AEs	Unselected Population	Thrombocytopenia:* 5.8% (GEF+CTX) vs 5.6% (CTX)	Rash: 3.6% (GEF+CTX) vs 1.1% (CTX)	Diarrhoea: 3.6% (GEF+CTX) vs 2.3% (CTX)	Thrombocytopenia:* 5.6% vs 5.8% Leukopenia: 2.5% vs 3.3% Diarrhoea: 2.3% vs 3.6%
INTACT2	Grade 3/4 CTC (V2) Common drug-related AEs	Unselected population	Diarrhoea: 9.9% (GEF+CTX) vs 2.9% (CTX)	Neutropenia: 6.7% (GEF+CTX) vs 5.9% (CTX)	Rash: 3.2% (GEF+CTX) vs 1.5% (CTX)	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 patients in either treatment group and at least a 5% difference between arms	Unselected population	Diarrhoea: 3.8% (GEF) vs 1.4% (CTX)	Any neutropenia: 3.7% (GEF) vs 67.1% (CTX)	Rash: 3.1% (GEF) vs 0.8% (CTX)	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 patients in either treatment group and at least a 5% difference between arms	EGFR only	ATE: 26.3% (GEF) vs 0.9% (CTX)	Rash: 5.3% (GEF) vs 2.7% (CTX)	Appetite loss: 5.3% (GEF) vs 6.2% (CTX)	Neutropenia: 65.5% vs 0.9% Arthralgia: 7.1% vs 0.9% Neuropathy: 6.2% vs 0% Appetite loss: 6.2% vs 5.3%
WJTOG3405	Grade >=3 CTC (V3) AEs occurred in 10% of either of the treatment groups	EGFR only	ALT/AST: 27.5% (GEF) vs 2.3% (CTX)	Rash: 2.3% (GEF) vs 0% (CTX)	Fatigue: 2.3% (GEF) vs 2.3% (CTX)	Neutropenia: 84% vs 0% Leucocytopenia: 50% vs 0% Anaemia: 17% vs 0%
Yu 2014	Grade 3+ Patients with at least 1 AE	Unselected population	Rash: 16% (GEF+CTX) vs 0% (CTX)	Vomiting: 10% (GEF) vs 8% (CTX)	Neutropenia: 10% (GEF) vs 12% (CTX)	Neutropenia: 12% vs 10% Nausea: 8% vs 5% Vomiting: 8% vs 10%
CETUXIMAB TRIALS						
BMS099	Grade 3/4 CTC (V3) Most frequent and relevant Grade 3/4 AEs	Unselected population	Neutropenia: 62.5% (CET+CTX) vs 56% (CTX)	Leukopenia: 43.8% (CET+CTX) vs 30.7% (CTX)	Fatigue: 15.1% (CET+CTX) vs 12.2% (CTX)	Same AEs as intervention
FLEX	Grade 3/4 CTC (V2) AEs that were reported in >5% of patients (G3/G4) or >1% (G4) or AEs of special interest in either group	EGFR expressing	Neutropenia: 53% (CET+CTX) vs 51% (CTX)	Leukopenia: 25% (CET+CTX) vs 19% (CTX)	Febrile neutropenia: 22% (CET+CTX) vs 15% (CTX)	Neutropenia: 52% (CTX) vs 52% CET+CTX Leukopenia: 19% (CTX) vs 25% (CET vs CTX) Anaemia: 16% (CTX) vs 1% (CET+CTX)

Footnotes

AE= adverse event; AFA=afatinib; ATE=aminotransferase elevation; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CET=cetuximab; CTC=common toxicity criteria; CTX=cytotoxic chemotherapy; ERL=erlotinib; GEF=gefitinib

*neutropenia was also reported as 5.8% for G3/4 as this rate was higher than the rate for all patients (5%) it was not included in the table; ** Rash listed as Grades A to D rather than 3 or 4

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Classification pending references

Data and analyses

1 Erlotinib versus Control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall Survival	5		Hazard Ratio(IV, Random, 95% CI)	Subtotals only
1.1.1 Erlotinib versus CTX	3		Hazard Ratio(IV, Random, 95% CI)	0.95[0.75, 1.22]
1.1.2 Erlotinib versus vinorelbine	1		Hazard Ratio(IV, Random, 95% CI)	2.16[0.58, 8.10]
1.1.3 Erlotinib plus CTX versus CTX plus placebo	1		Hazard Ratio(IV, Random, 95% CI)	0.48[0.27, 0.85]
1.2 Progression Free Survival	6		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
1.2.1 Erlotinib versus CTX	4		Hazard Ratio(IV, Fixed, 95% CI)	0.30[0.24, 0.38]
1.2.2 Erlotinib versus vinorelbine	1		Hazard Ratio(IV, Fixed, 95% CI)	0.55[0.21, 1.46]
1.2.3 Erlotinib plus CTX versus CTX plus placebo	1		Hazard Ratio(IV, Fixed, 95% CI)	0.25[0.16, 0.39]
1.2.4 Erlotinib versus CTX (sensitivity analysis using ENSURE independent review data)	4		Hazard Ratio(IV, Fixed, 95% CI)	0.33[0.26, 0.42]
1.3 Tumour response	7		Risk Ratio(M-H, Random, 95% CI)	Subtotals only
1.3.1 Erlotinib versus CTX	5	593	Risk Ratio(M-H, Random, 95% CI)	2.20[1.53, 3.17]
1.3.2 Erlotinib versus vinorelbine	1	24	Risk Ratio(M-H, Random, 95% CI)	0.83[0.19, 3.67]
1.3.3 Erlotinib versus erlotinib plus CTX	0	0	Risk Ratio(M-H, Random, 95% CI)	Not estimable
1.3.4 Erlotinib plus CTX versus CTX plus placebo	1	97	Risk Ratio(M-H, Random, 95% CI)	5.74[2.86, 11.50]

2 Gefitinib versus CTX

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Overall survival	4		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
2.1.1 Gefitinib versus gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	1.04[0.50, 2.20]
2.1.2 Gefitinib versus paclitaxel plus carboplatin	2		Hazard Ratio(IV, Fixed, 95% CI)	0.95[0.77, 1.18]
2.1.3 Gefitinib versus docetaxel plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	1.25[0.88, 1.78]
2.2 Progression free survival	4		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
2.2.1 Gefitinib versus gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.54[0.27, 1.10]
2.2.2 Gefitinib versus paclitaxel plus carboplatin	2		Hazard Ratio(IV, Fixed, 95% CI)	0.39[0.32, 0.48]
2.2.3 Gefitinib versus docetaxel plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.49[0.34, 0.71]
2.3 Tumour response	4	648	Risk Ratio(M-H, Fixed, 95% CI)	1.87[1.60, 2.19]
2.3.1 Gefitinib versus gemcitabine plus cisplatin	1	42	Risk Ratio(M-H, Fixed, 95% CI)	2.26[1.17, 4.34]
2.3.2 Gefitinib versus paclitaxel plus carboplatin	2	489	Risk Ratio(M-H, Fixed, 95% CI)	1.83[1.54, 2.18]
2.3.3 Gefitinib versus docetaxel plus cisplatin	1	117	Risk Ratio(M-H, Fixed, 95% CI)	1.93[1.26, 2.94]

3 Afatinib versus CTX

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Overall survival	2		Hazard Ratio(IV, Fixed, 95% CI)	0.93[0.74, 1.17]
3.1.1 Afatinib versus pemetrexed plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.91[0.66, 1.25]
3.1.2 Afatinib versus gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.95[0.68, 1.33]
3.2 Progression free survival	2		Hazard Ratio(IV, Random, 95% CI)	0.41[0.20, 0.83]
3.2.1 Afatinib versus pemetrexed plus cisplatin	1		Hazard Ratio(IV, Random, 95% CI)	0.58[0.43, 0.78]
3.2.2 Afatinib versus gemcitabine plus cisplatin	1		Hazard Ratio(IV, Random, 95% CI)	0.28[0.20, 0.39]
3.3 Tumour response	2	709	Risk Ratio(M-H, Fixed, 95% CI)	2.71[2.12, 3.46]
3.3.1 Afatinib versus pemetrexed plus cisplatin	1	345	Risk Ratio(M-H, Fixed, 95% CI)	2.48[1.74, 3.54]
3.3.2 Afatinib versus gemcitabine plus cisplatin	1	364	Risk Ratio(M-H, Fixed, 95% CI)	2.92[2.08, 4.09]

4 Cetuximab plus CTX versus CTX

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Overall survival	2		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
4.1.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	1.62[0.54, 4.84]
4.1.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	1.48[0.77, 2.82]
4.2 Progression free survival	2		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
4.2.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	1.17[0.36, 3.80]
4.2.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.92[0.53, 1.60]
4.3 Tumour response	2	81	Risk Ratio(M-H, Fixed, 95% CI)	1.43[0.83, 2.47]
4.3.1 Cetuximab plus paclitaxel or docetaxel plus carboplatin versus paclitaxel or docetaxel plus carboplatin	1	17	Risk Ratio(M-H, Fixed, 95% CI)	4.50[0.63, 32.38]
4.3.2 Cetuximab plus vinorelbine plus cisplatin versus vinorelbine plus cisplatin	1	64	Risk Ratio(M-H, Fixed, 95% CI)	1.19[0.67, 2.11]

5 Erlotinib versus CTX

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Overall survival	3		Hazard Ratio(IV, Fixed, 95% CI)	0.96[0.75, 1.23]
5.1.1 Erlotinib versus gemcitabine plus cisplatin	2		Hazard Ratio(IV, Fixed, 95% CI)	1.00[0.71, 1.40]
5.1.2 Erlotinib versus docetaxel plus cisplatin or gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.91[0.63, 1.31]

5.2 Progression free survival	4		Hazard Ratio(IV, Fixed, 95% CI)	0.29[0.24, 0.35]
5.2.1 Erlotinib versus gemcitabine plus carboplatin	2		Hazard Ratio(IV, Fixed, 95% CI)	0.24[0.18, 0.33]
5.2.2 Erlotinib versus gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.60[0.30, 1.19]
5.2.3 Erlotinib versus docetaxel plus cisplatin or gemcitabine plus cisplatin	1		Hazard Ratio(IV, Fixed, 95% CI)	0.34[0.23, 0.50]
5.2.4 Erlotinib versus gemcitabine plus carboplatin (sensitivity analysis using ENSURE independent review data)	2		Hazard Ratio(IV, Fixed, 95% CI)	0.27[0.19, 0.37]
5.3 Tumour response	5	593	Risk Ratio(M-H, Fixed, 95% CI)	2.26[1.85, 2.76]
5.3.1 Erlotinib versus gemcitabine plus carboplatin	2	371	Risk Ratio(M-H, Fixed, 95% CI)	2.05[1.65, 2.56]
5.3.2 Erlotinib versus gemcitabine plus cisplatin	1	39	Risk Ratio(M-H, Fixed, 95% CI)	1.68[0.67, 4.24]
5.3.3 Erlotinib versus docetaxel plus cisplatin or gemcitabine plus cisplatin	1	173	Risk Ratio(M-H, Fixed, 95% CI)	3.89[2.28, 6.63]
5.3.4 Erlotinib versus vinorelbine plus carboplatin	1	10	Risk Ratio(M-H, Fixed, 95% CI)	0.33[0.04, 2.56]

6 Erlotinib plus CTX versus CTX plus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Overall Survival	1		Hazard Ratio(IV, Fixed, 95% CI)	0.48[0.27, 0.85]
6.1.1 Erlotinib plus gemcitabine plus carboplatin or cisplatin versus gemcitabine plus carboplatin or cisplatin plus placebo	1		Hazard Ratio(IV, Fixed, 95% CI)	0.48[0.27, 0.85]
6.2 Progression Free Survival	1		Hazard Ratio(IV, Fixed, 95% CI)	0.25[0.16, 0.39]
6.2.1 Erlotinib plus gemcitabine plus carboplatin or cisplatin versus gemcitabine plus carboplatin or cisplatin plus placebo	1		Hazard Ratio(IV, Fixed, 95% CI)	0.25[0.16, 0.39]
6.3 Tumour response	1	97	Risk Ratio(M-H, Fixed, 95% CI)	5.74[2.86, 11.50]
6.3.1 Erlotinib plus gemcitabine plus carboplatin or cisplatin versus gemcitabine plus carboplatin or cisplatin plus placebo	1	97	Risk Ratio(M-H, Fixed, 95% CI)	5.74[2.86, 11.50]

7 Erlotinib versus vinorelbine

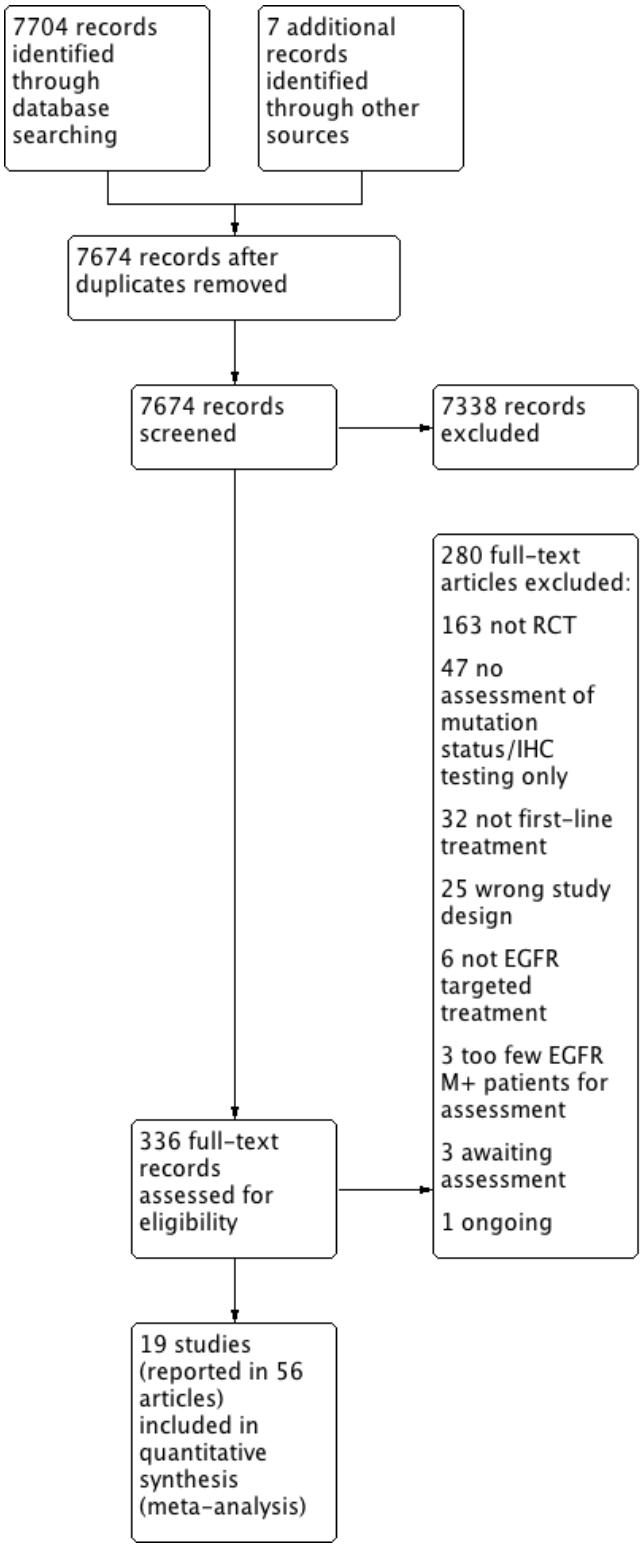
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Overall survival	1		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
7.1.1 Erlotinib versus vinorelbine	1		Hazard Ratio(IV, Fixed, 95% CI)	2.16[0.58, 8.10]
7.2 Progression free survival	1		Hazard Ratio(IV, Fixed, 95% CI)	Subtotals only
7.2.1 Erlotinib versus vinorelbine	1		Hazard Ratio(IV, Fixed, 95% CI)	0.55[0.21, 1.46]
7.3 Tumour response	1		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.3.1 Erlotinib versus vinorelbine	1	24	Risk Ratio(M-H, Fixed, 95% CI)	0.83[0.19, 3.67]

8 Gefitinib plus CTX versus CTX

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Progression-free survival	1		Hazard Ratio(IV, Fixed, 95% CI)	0.20[0.05, 0.75]
8.2 Tumour response	1	31	Risk Ratio(M-H, Fixed, 95% CI)	1.54[0.89, 2.67]

Figures

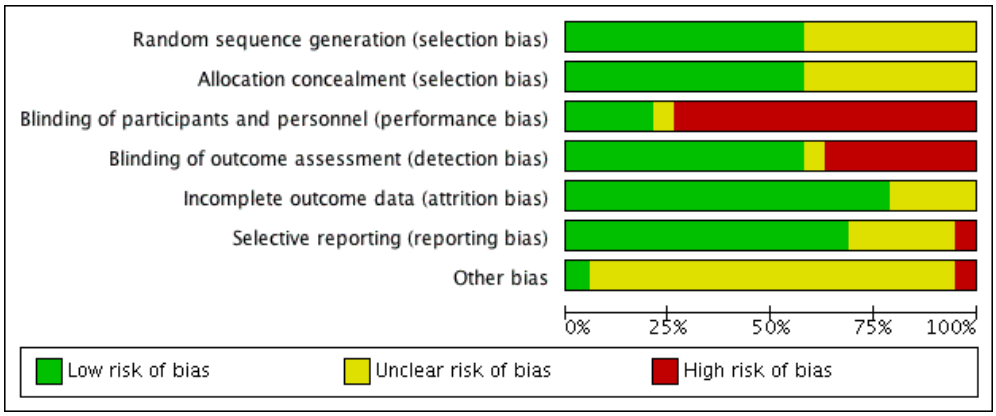
Figure 1



Caption

Study flow diagram.

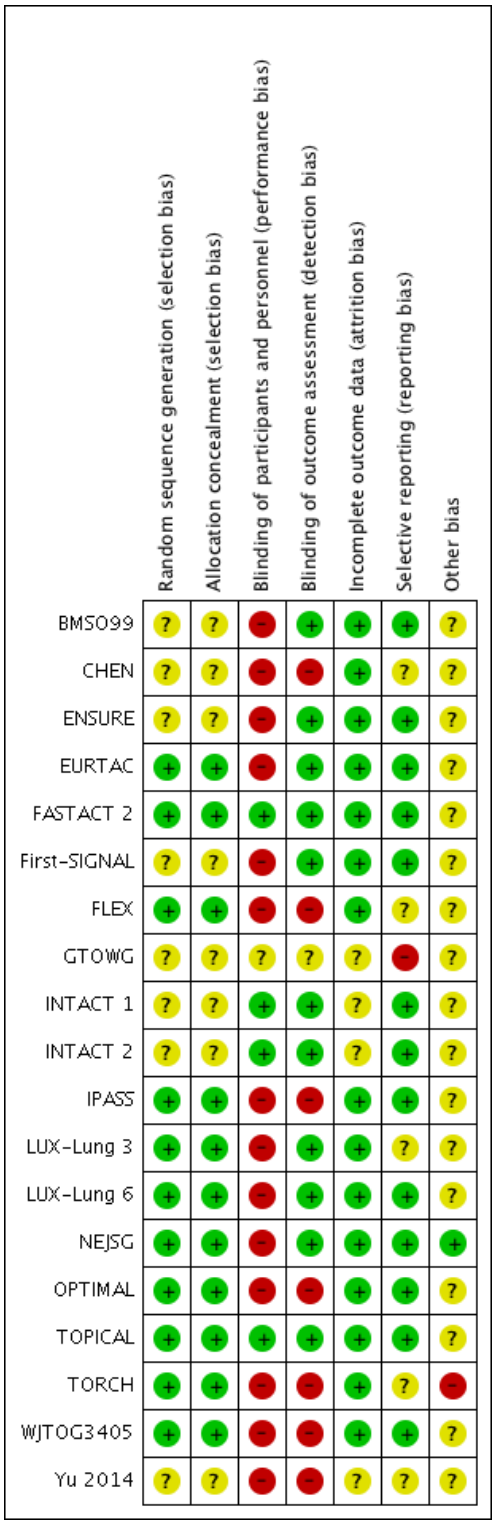
Figure 2



Caption

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

Figure 3



Caption

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

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices

1 MEDLINEedline (via OvidVID; 1946 onwards)

1 exp Carcinoma, Non-Small-Cell Lung/
2 (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.
3 (erlotinib or tarceva).af.
4 (gefitinib or iressa).af.
5 (tyrosine kinase inhibit$ or monoclonal antibod$ or EGFR).tw.
6 1 or 2
7 or/3-5
8 6 and 7
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.
11 randomized.ab.
12 placebo.ab.
13 clinical trials as topic.sh.
14 randomly.ab.
15 trial.ti.
16 or/9-15
17 exp animals/ not humans.sh.
18 16 not 17
19 8 and 18

2 Updated search strategy

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung càncer
(date: Feb 5th, 2014)

Ovid MEDLINE(R) <1946 to January Week 4 2014>

1 exp Carcinoma, Non-Small-Cell Lung/ (30107)
2 (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab. (29454)
3 nsclc.ti,ab. (16188)
4 1 or 2 or 3 (36222)
5 (tyrosine kinase inhibit$ or monoclonal antibod$ or EGFR or TKI$).tw. (183400)
6 (erlotinib or tarceva).af. (3081)
7 (gefitinib or iressa).af. (3928)
8 (afatinib or gilotrif).af. (65)
9 5 or 6 or 7 or 8 (185552)
10 4 and 9 (5109)
11 randomized controlled trial.pt. (359493)
12 controlled clinical trial.pt. (86909)
13 randomized.ab. (260696)
14 placebo.ab. (141221)
15 drug therapy.fs. (1651531)
16 randomly.ab. (186387)
17 trial.ab. (268187)
18 groups.ab. (1203305)
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (3092194)
20 exp animals/ (16958091)
21 humans.sh. (13090537)
22 20 not 21 (3867554)
23 19 not 22 (2628643)
24 10 and 23 (3449)
25 10 and 23 (3449)
26 limit 25 to yr="2012 -Current" (760)

Ovid Embase <1996 to 2014 February 14>

1 exp lung non small cell cancer/ (55263)
2 (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab. (44493)
3 nsclc.ti,ab. (29792)
4 1 or 2 or 3 (62940)
5 (tyrosine kinase inhibit$ or monoclonal antibod$ or EGFR or TKI$).tw. (152359)
6 (erlotinib or tarceva).af. (15970)
7 (gefitinib or iressa).af. (15976)
8 (afatinib or gilotrif).af. (707)
9 5 or 6 or 7 or 8 (166496)
10 4 and 9 (14716)
11 random:.tw. or placebo:.mp. or double-blind:.mp. (900038)

12 10 and 11 (2814)
13 10 and 11 (2814)
14 limit 13 to yr="2012 -Current" (765)

Cochrane Central Register of Controlled Trials : Issue 1 of 12, January 2014

#1MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees2303
#2lung:ti,ab 18465
#3(cancer* or carcin* or neoplasm* or tumour* or tumor*):ti,ab 69595
#4(non-small or nonsmall):ti,ab 4068
#5#2 and #3 and #4 4012
#6nsclc:ti,ab 2450
#7#1 or #5 or #6 4416
#8(tyrosine kinase inhibit* or monoclonal antibod* or EGFR or TKI*):ti,ab 3127
#9(erlotinib or tarceva):ti,ab 245
#10(gefitinib or iressa):ti,ab 213
#11(afatinib or gilotrif):ti,ab 19
#12#8 or #9 or #10 or #11 3406
#13#7 and #12 399
#14#7 and #12 from 2012 to 2014135

3 Search strategy 3

Ovid EMBASE April 2014 until 1st June 2015 and 1946 to 1st June

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