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Evidence-Based Series #7-9 Version 2 BEING UPDATED

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung, and the Lung Disease Site Group (DSG)

Report Date: May 8, 2014

An assessment conducted in December 2017 indicated that Evidence-based Series (EBS) 7-9 Version 2 will be UPDATED. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 7-9 v2 is comprised of 3 sections and is available on the CCO Lung Cancer page:

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development, and External Review Process**

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PEBC Report Citation (Vancouver Style): Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC; Lung Disease Site Group. Use of the epidermal growth factor receptor inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib in the treatment of non-small-cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario; 2014 Apr 23 [Being Updated 2017 Dec]. Program in Evidence-based Care Evidence-based Series No.: 7-9 Version 2 BEING UPDATED.

Journal Citations (Vancouver Style): Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review. Curr Oncol. 2015 Jun;22(3):e183-215.

Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. J Thorac Oncol. 2006 May;1(4):367-76.

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Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2006	1966 to November 2005	Full Report	Peer review publication. Web publication.	Not Applicable
Version 2 2013	2005 to March 2014	New data and old data integrated in new Full Report	Updated web publication.	Not Applicable

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Evidence-Based Series #7-9 Version 2: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO

Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline Guideline Recommendations

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung, and the Lung DSG

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Report Date: May 8, 2014

QUESTIONS

1. In patients with advanced non-small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)?

2. In patients with advanced NSCLC who have progressed on platinum-based chemotherapy, does subsequent therapy with EGFR inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib improve overall survival or PFS? Is there a preferred sequence for second-line therapy with an EGFR inhibitor or chemotherapy?

3. In patients with advanced stage IIIB or IV NSCLC who have received initial first-line platinum-based chemotherapy, does maintenance therapy with erlotinib, gefitinib, afatinib, dacomitinib or icotinib improve overall survival or PFS?

4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?

TARGET POPULATION

This practice guideline applies to adult patients with advanced (stage IIIB or IV) non-small-cell lung cancer.

INTENDED USERS

This guideline is targeted for clinicians involved in the delivery of systemic treatment for cancer patients.

RECOMMENDATIONS AND KEY EVIDENCE

Recommendation 1a

First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients.

The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations.

Key Evidence

Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients (1-26).

Recommendation 1b

In patients with EGFR mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib or afatinib is the preferred treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer PFS and improved quality of life.

Qualifying Statement

There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative.

Key Evidence

Seven randomized trials and two meta-analyses comprised the evidence base. The trials and meta-analyses based on data from these trials showed that PFS was prolonged in molecularly selected patients when an EGFR was used as first-line treatment (27-33).

- Six trials were included in the initial meta-analysis that showed a hazard ratio (HR) of 0.35 (95% confidence interval (CI), 0.28-0.45; p<0.00001) (27-30,32,33).
- A second meta-analysis done on PFS that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.38 (95% CI, 0.31-0.44; p<0.00001) (20,21,28-30,32-34).
- All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy (28-34).

Recommendation 2

In patients well enough to consider second-line chemotherapy, an EGFR TKI can be recommended as second- or third-line therapy.

There is insufficient evidence to recommend the use of a second EGFR TKI, such as afatinib, in patients whose disease has progressed following chemotherapy and gefitinib or erlotinib, as available data does not demonstrate any improvement in overall survival

Qualifying Statements

There are data to support the use of an EGFR TKI in patients who have progressed on platinum-based chemotherapy. Erlotinib is known to improve overall survival and quality of life when used as second- or third-line therapy, in comparison to best supportive care.

However, available data would suggest that second-line therapy with either chemotherapy or an EGFR TKI results in similar PFS and overall survival. Available evidence would support the use of either erlotinib or gefitinib in this situation.

Data from a randomized phase II trial suggests improved PFS for dacomitinib versus (vs) erlotinib, but these data require confirmation in a phase III trial.

The Lux Lung 1 study failed to meet its primary outcome of improved overall survival. However, the study showed improved PFS for patients randomized to afatinib and was associated with improvements in lung cancer symptoms.

Key Evidence

- Three studies examined an EGFR inhibitor as a second-line treatment against a placebo and best supportive care (35-37). One study reported on the use of erlotinib and showed a significant improvement in PFS (p=0.001) and overall survival (p=0.001) (35). The other two studies evaluated gefitinib, with one study finding significant results for response rate (p<0.0001) (37) and the other for PFS (p=0.002) (36).
- A meta-analysis done on seven second-line studies showed no improvement with EGFR TKIs vs chemotherapy for progression-free survival (HR, 0.99; 95% CI 0.86-1.12, p=0.67) and overall survival (HR, 1.02; 95% CI, 0.95-1.09, p=0.56) (38-44)
- One phase II study that compared erlotinib to dacomitinib (45)showed significant results for dacomitinib for response rate (p=0.011) and for PFS (p=0.012).
- The Lung Lux 1 study examined the use of afatinib in the third- and fourth-line setting against a placebo. This study showed improved PFS (HR, 0.38; 95% CI, 0.31-0.48, p<0.0001) but no difference in overall survival (HR, 1.08; 95% CI, 0.86-1.35, p=0.74) (46).

Recommendation 3

An EGFR TKI is recommended as an option for maintenance therapy in patients who have not progressed after four cycles of a platinum-doublet chemotherapy. No recommendation can be made with respect to the choice of gefitinib or erlotinib.

Qualifying Statements

- Trials have evaluated both erlotinib and gefitinib, but no trials directly compare these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the overall survival advantage is modest for both agents.
- There are competing strategies of maintenance chemotherapy without an EGFR TKI, such as pemetrexed, that are not addressed in this guideline. The recommendation

for TKI above should not be taken as excluding these other strategies as reasonable options; as this evidence was not reviewed, no statement can be made for or against these other strategies. The Lung Disease Site Group (DSG) plans to develop a separate guideline on maintenance therapy as soon as possible.

- This recommendation applies to both EGFR mutation positive and wild-type patients.

Key Evidence

Six studies evaluated the use of an EGFR inhibitor in the maintenance setting (47-52).

- Two of the trials reported a statistically significant survival benefit with erlotinib: one for response rate ($p=0.0006$) when compared to placebo (47) and one for progression-free survival when combined with bevacizumab against bevacizumab alone ($p<0.001$) (51).
- One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs 7%) and 9.1 months vs 8.3 months for overall survival (50).
- Two trials evaluating gefitinib found a statistically significant benefit for PFS in the maintenance setting, $p<0.001$ when combined with chemotherapy and against chemotherapy (48) and $p<0.0001$ compared to a placebo (49).
- Another trial evaluated gefitinib and showed a higher response rate, but this was not significant ($p=0.369$) (52).

Recommendation 4

The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity.

Key Evidence

- Two randomized phase II trials (53-54), each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients) (53).
- One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib (45).
- One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs 8%) (54).

RELATED GUIDELINES

A previous version of this guideline is contained in: Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. J Thorac Oncol. 2006;1(4):367-76.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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Evidence-Based Series #7-9 Version 2: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non–Small-Cell Lung Cancer: A Clinical Practice Guideline Evidentiary Base

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung and the Lung DSG.

Report Date: May 8, 2014

QUESTIONS

1. In patients with advanced non–small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, PFS, response rate and quality of life)?

2. In patients with advanced NSCLC who have progressed on platinum-based chemotherapy, does subsequent therapy with EGFR inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib improve overall survival or PFS? Is there a preferred sequence for second-line therapy with an EGFR inhibitor or chemotherapy?

3. In patients with advanced stage IIIB or IV NSCLC who have received initial first-line platinum-based chemotherapy, does maintenance therapy with erlotinib, gefitinib, afatinib, dacomitinib or icotinib improve overall survival or PFS?

4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?

INTRODUCTION

Lung cancer represents a major health burden in Canada. There were approximately 25,600 new cases and over 20,000 deaths from lung cancer in Canada during 2012. Many of those affected present with advanced disease and are candidates for palliative systemic therapy (1). Historically a similar approach was undertaken in all patients with advanced non-small-cell lung cancer (NSCLC), whereby platinum-doublets were recommended as initial, or first-line therapy (2,3), pemetrexed (4) or docetaxel (5,6) as second-line therapy and erlotinib as second- or third-line therapy (7,8).

Significant changes have taken place in the approach to treatment of advanced NSCLC over the last five years. Treatment algorithms are now heavily influenced by the histologic subtype of NSCLC (9). A previous version of this guideline produced by the PEBC

recommended the use of erlotinib as third-line therapy, or as second-line therapy in patients who are not candidates for second-line chemotherapy (7). Multiple trials have since been conducted examining the sequence of subsequent lines of therapy (EGFR TKI versus [vs] chemotherapy). More importantly, the discovery of molecular abnormalities, such as mutations of the epidermal growth factor receptor (EGFR) (10,11) and translocations of the anaplastic lymphoma kinase (ALK) (12) gene have identified a group of patients who appear to derive significantly greater benefit from molecularly targeted therapies.

This guideline examines the expanded use of EGFR tyrosine kinase inhibitors (EGFR TKI). Previously, these agents were recommended as a last line of therapy. The current guideline addresses questions about the sequence of EGFR TKIs and chemotherapy. Additionally, the guideline addresses the question of whether special populations, defined by clinical characteristics (Asian ethnicity, female sex, adenocarcinoma histology, age or smoking status), or molecular characteristics (presence of activating mutations of the EGFR gene, EGFR gene copy number, or EGFR protein overexpression, should influence the recommendations concerning the use of EGFR TKIs.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (13). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by four clinical members of the PEBC Lung DSG and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the role of the epidermal growth factor receptor (EGFR) inhibitors including gefitinib, erlotinib, afatinib, dacomitinib or icotinib in the treatment of patients with non-small-cell lung cancer (NSCLC). The body of evidence in this review is primarily comprised of mature, randomized controlled trial data. This evidence forms the basis of the recommendations developed by the Lung DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Strategy

The MEDLINE (2006 to March 2014), EMBASE (2006 to March 2014) and Cochrane Library (March 2014) databases were searched for published practice guidelines, systematic reviews, and randomized clinical trials. Reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase (http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm), the National Guidelines Clearinghouse (http://www.guideline.gov/) and other Web sites were searched for existing evidence-based practice guidelines. The American Society of Clinical Oncology (ASCO) Conference proceedings from 2007-2013 were searched. Search terms indicative of NSCLC, gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib were used. The full search strategy is available in Appendix A, and the search flow diagram is available in Appendix B. Articles included in this version of the guideline prior to 2006 were found using the search strategy in the previous version of this guideline (7). Only fully published articles from the previous version of this guideline were included.

Study Selection Criteria

Inclusion Criteria

1. Practice guidelines on the use of gefitinib, erlotinib, afatinib, dacomitinib or icotinib as treatment for NSCLC; or
2. Meta-analyses or randomized trials (phase II or phase III) comparing gefitinib, erlotinib, afatinib, dacomitinib or icotinib, alone or in combination with chemotherapy, to placebo, best supportive care, or chemotherapy, or comparing different doses or schedules of gefitinib, erlotinib, afatinib, dacomitinib or icotinib; and
3. Fully published papers or published abstracts of trials in any language that reported at least one of the following outcomes by treatment group: symptom control, quality of life, tumour response rate, survival or toxicity.

Exclusion Criteria

1. Pilot trials, dose-escalation trials, or case series (including expanded access programs) studies.
2. Letters and editorials that reported clinical trial outcomes.
3. Conference abstracts before 2007.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data were pooled using the Review Manager software (RevMan 5.1.6) provided by the Cochrane Collaboration (14). Since hazard ratios (HRs), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (15), those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CIs) using the methods described by Parmar et al (15). A random effects model was used for all pooling.

Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% confidence intervals (CI). An HR <1.0 indicates that patients receiving gefitinib, erlotinib, afatinib, dacomitinib or icotinib had a higher probability of experiencing an event; conversely, an HR >1.0 suggests that patients receiving erlotinib or gefitinib experienced a lower probability of an event.

RESULTS

Literature Search Results

Articles were selected for consideration in this systematic review of the evidence if they were published reports of randomized controlled trials. A total of 3633 English and foreign-language studies were identified. Ninety-six randomized trials met the pre-defined eligibility criteria for this systematic review. Of those, 66 were fully published reports, and 30 were in abstract form, including four updates to fully published trials. Data from slide presentations associated with abstract trial reports were also included if the presentations were publicly available on meeting Web sites and provided additional data. Single-arm prospective trials were included in an earlier version of this report but not the current version (7). No relevant systematic reviews or evidence-based clinical practice guidelines that answered our research questions were identified.

Study/Trial Design and Quality

Thirty-six phase III RCTs were identified. Thirty were fully published papers (8,16-44)

and six were abstracts (45-50). There was one fully published phase IIb/III trial (51).

There are 55 randomized phase II trials, of which 38 are fully published papers (52-89) and 17 abstracts (90-106). The results of these phase II studies must be interpreted with caution due to the methodological limitations associated with phase II studies. One phase II study was non-comparative and was done to see if further research was warranted (80). One study was initiated to assess safety only (71). Another study was not powered to pick up treatment differences, and one was only interested in symptom improvement (57).

Forty-nine fully published papers were supported by industry grants, 14 were led by cooperative groups or government grants, five were a combination of industry and cooperative groups, and two trials did not state the funding source. The method of randomization was reported in 32 fully published papers. Details of the study quality for fully published trials can be found in Appendix C.

OUTCOMES

This report is broken down into three populations of NSCLC patients (unselected, clinically selected, molecularly selected). In the unselected group, any NSCLC patient was allowed to participate in the trial as long as they met the other trial eligibility criteria in the absence of molecular testing. In the clinically selected group, patients were selected based on clinical characteristics predictive of an EGFR mutation such as Asian ethnicity, adenocarcinoma histology, female sex, smoking status or age. In the molecularly selected group, patients were included if their tumours tested positive for an EGFR mutations.

First-Line Treatment

Unselected Population

There are 22 trials that examine the use of an EGFR inhibitor in unselected patients with stage IIIB/IV non–small-cell lung cancer. There are 16 fully published trials (19,20,22,23,38,42,53,56,59,60,68,70,72,73,77,80) and six abstracts (46,48,90,98,99,102). A meta-analysis was not done in this population due to the lack of clinical homogeneity.

First-line EGFR Inhibitor Versus Chemotherapy in Unselected Patients

Six fully published papers and three abstracts compared an EGFR inhibitor to platinum-based chemotherapy. These results can be seen in Table 1. The majority of these trials are small trials with fewer than 100 patients per arm. Only the TORCH trial appears to have a sufficient number of participants to provide meaningful information on overall survival (20).

The response rate was not reported in three studies. In one study, response rate favoured the EGFR inhibitor (53), and in four studies it favoured chemotherapy (20,56,68,99). The study by Reck et al found a significantly higher response rate in patients randomized to chemotherapy (p=0.0001) (99).

The results favour improved PFS for patients randomized to chemotherapy. Median PFS was similar in two trials (56,73). In one trial, PFS was longer in the EGFR-inhibitor group: 4.57 months for erlotinib vs 2.53 months for vinorelbine (HR, 0.6444; 95% CI, 0.4325-0.9601, p=0.0308) (53). In five trials, PFS was longer in the chemotherapy group (20,68,70,90,99). Several of these trials found PFS to be significant in favour of chemotherapy (20,70,99). One trial examined time to progression and found that it was longer with chemotherapy, but this result was not significant (68).

One trial reported non-significant improvements in overall survival in the EGFR inhibitor group (53). In seven trials, overall survival was prolonged with chemotherapy (20,56,68,70,73,90,99). In the largest trial, the TORCH trial, overall survival was significantly worse for patients randomized to erlotinib (20). These findings raise the possibility that initial

therapy with an EGFR TKI agent in an unselected population of patient with advanced NSCLC may be inferior treatment.

Quality of life and symptom control were discussed in three trials (53,56,90). In the trial by Crino et al, the EGFR inhibitor gefitinib group scored higher on all four of the quality of life assessment tools (Table 2). The trials by Agarwal et al and Chen et al found no difference in quality of life, although the patients in the erlotinib group in the Chen et al trial had significantly better physical well-being (53,90).

The most significant toxicities from EGFR inhibitors are diarrhea and rash (Table 2). Most other adverse effects were mild and occurred at similar rates across trials, with the exception of neutropenia, which occurred more commonly in the chemotherapy arm.

First-line EGFR Inhibitor Plus Chemotherapy Versus Chemotherapy in Unselected Patients

Eight trials examined the use of a first-line EGFR inhibitor plus chemotherapy vs chemotherapy in unselected patients (Table 3). Six are fully published (19,22,23,38,72,77), and two are abstracts (48,98). There was no significant difference in response rate in four trials involving over 4000 patients (19,22,23,38). In three additional trials, the response rate is in favour of the EGFR inhibitor group (19,22,23,38,48,72,77). In the trial by Riely et al, the response rate was the highest (34%) in the 1500 mg/day erlotinib followed by the paclitaxel and carboplatin arm. The response rate was 18% in the arm where the dose of erlotinib was 150mg and 28% in the paclitaxel and carboplatin followed by 1500mg/day of erlotinib (77).

PFS was reported in three trials, which all reported a longer PFS in the combined EGFR inhibitor and chemotherapy groups (22,48,72). Statistical significance was reported in two of the trials, which both favoured the EGFR and chemotherapy groups (48,72). Four trials reported on time to progression (19,23,38,39,77). The INTACT I/II, TRIBUTE and TALENT trials all showed no significant difference in time to progression across all arms (19,23,38). The trial by Riely et al did not show an increase in time to progression between the 150 and 1500 mg/day erlotinib doses, followed by paclitaxel and carboplatin: both groups had a four-month time to progression. The combination of paclitaxel and carboplatin followed by 1500 mg/day of erlotinib showed an increase in time to progression by one month (77). An unplanned subgroup analysis on mutation status was done in the TRIBUTE trial for patients with available tissue. There was an increase in time to progression with erlotinib plus paclitaxel and carboplatin (12.5 months) compared to chemotherapy alone (6.6 months). However this difference did not reach significance (p=0.092) (23).

There was no clear improvement in overall survival for the addition of an EGFR TKI to chemotherapy. Statistical significance was not reached in any trial. In the trial by Riely et al, the 1500 mg/day erlotinib dose followed by paclitaxel and carboplatin had the greatest survival of 15 months compared to 10 months for both the 150 mg/day of erlotinib followed by paclitaxel and carboplatin and paclitaxel and carboplatin followed by 1500 mg/day of erlotinib (77). A trend towards longer overall survival was observed in the FAST-ACT II trial, favouring the chemotherapy plus erlotinib (HR, 0.78; 95%CI, 0.60-1.02, p=0.069) (48). These results do not support the addition of an EGFR TKI to platinum-based chemotherapy.

Toxicities were similar between the two groups, with the exception of diarrhea and skin disorders, which occurred more frequently in the EGFR inhibitor groups (Table 4).

Table 1. EGFR inhibitor vs chemotherapy in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Kobayashi 2009 (abstr)(46) phase 3	NSCLC PS 0-1 No prior chemotherapy	80 75	Gefitinib 250 mg/day Carboplatin AUC 6 + paclitaxel 200mg/m^2	Prelim. RR: 53.7% (both groups analyzed together)	6.5 months (both groups were analyzed together)	NR
Gridelli 2012 TORCH(20) phase 3	Stage IIIB/IV NSCLC PS 0-1 Patients at first diagnosis and those with recurrence were eligible	380 380	Erlotinib 150mg/day Cisplatin 80 mg/m^2 + Gemcitabine 1200 mg/m^2	20.3% 32.6%	6.4 months 8.9 months HR 1.21; 95% CI 1.04-1.42	8.7 months 11.6 months HR 1.22; 95% CI 1.03-1.44
Crino 2008 INVITE (56) phase 2	Elderly patients ≥70; Stage IIIB/IV NSCLS; No chemo or EGFR therapy; PS 0-2	97 99	Gefitinib 250 mg/day Vinorelbine 30mg/m^2	3.1% 5.1%	2.7 months 2.9 months HR 1.19; 95% CI 0.85-1.65, p=0.310	5.9 months 8.0 months HR 0.98%; 95% CI 0.66-1.47, p=0.272
Lilenbaum 2008 (70) phase 2	Stage IIIB or IV NSCLC PS 2 No prior chemotherapy or EGFR therapy	52 51	Erlotinib 150mg/day Carboplatin AUC6 + paclitaxel 200mg/m^2	NR	1.91 months 3.52 months HR 1.45 95% CI 0.98-2.15, p=0.063	6.6 months 95% CI 3.78-8.25 9.5 months 95% CI 1.94-12.45
Agarwal 2010 (abstr)(90) phase 2	NSCLC PS 2 only Chemo-naïve Stage IIIB-IV	18 17	Gefitinib 250 mg/day Carboplatin AUC 5 + gemcitabine 1000 mg/m^2	NR	42 days 95% CI 35-90 131 days 95% CI 66-190	138 days 95% CI 63-268 213 days 95% CI 101-399
Morere IFCT-0301 2010 (73) phase 2	Stage IIIB/IV NSCLC; no prior therapy; PS 2 or 3	43/43 42/41 42/41	Gefitinib 250 mg/day Gemcitabine 1250 mg/m^2 Docetaxel 75mg/m^2	NR	1.9 months 2.0 months 2.0 months Gemcitabine vs. Gefitinib p=0.172 Docetaxel vs Gefitinib p=0.078 Docetaxel vs gemcitabine p=0.633	2.2 months 2.4 months 3.5 months Gemcitabine vs. Gefitinib p=0.190 Docetaxel vs Gefitinib p=0.088 Docetaxel vs gemcitabine p=0.706

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Reck 2010 (Abstr) (99) phase 2	Age ≥70 years advanced NSCLC stage IIIB/IV	144 140	Erlotinib 150mg/day Carboplatin AUC 5 plus Vinorelbine 25 mg/m^2	7.8% 28.3% (p= 0.0001)	2.4 months 4.6 months (HR 1.6; 75% CI 1.22-2.09, p: 0.0005)	7.3 months 8.4 months, HR 1.24; 75% CI 0.9-1.71)
LeCaer 2011 GFPC 0504 study(68) phase 2	IIIB/IV NSCLC Fit elderly patents 65-89 years No previous treatment with chemotherapy Live expectancy > 3 months	51 48	Erlotinib 150mg/day Docetaxel 30 mg/m^2 and Gemcitabine 900 mg/m^2 Reverse on relapse	1st line 17.6% 2nd line 11.8% 1st line 20.8% 2nd line 6.3%	TTP1 2.7 months TTP2 5.8 months TTP1 4.7 months TTP2 7.5 months TTP1 & 2 p=0.53	7.1 months 9.4 months
Chen 2012 (53) phase 2	Inoperable stage IIIB/IV NSCLC Age ≥70 years PS 0-3 Chemo-naive	57 56	Erlotinib 150mg/day Vinorelbine 60mg/m^2	22.8% 8.9%	4.57 months 2.53 months HR 0.6444; 95% CI 0.4325-0.9601, p=0.0308	11.67 months 9.3 months p=0.6975

Abbreviations: AUC = area under curve; Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; NSCLC = non–small-cell lung cancer; NR = not reported; PS = performance status; TTP – time to progression.

Table 2. Quality of life and adverse effects in EGFR inhibitor vs chemotherapy in unselected patients.

Reference	Treatment	Number enrolled/ analyzed	Symptom control/Quality of Life	Adverse effects		
Kobayashi 2009 (abstr) (46) phase 3	Gefitinib 250 mg/day Carboplatin AUC 6 + Paclitaxel 200mg/m^2	80 75	NR	Grades 3 & 4 (%) Neutropenia Liver dysfunction Neuropathy	G 1(1) 24(30) 0	C+P 29 (39) 1 (1) 5 (7)
Gridelli 2012 TORCH(20) phase 3	Erlotinib 150mg/day Cisplatin 80 mg/m^2 and Gemcitabine 1,200 mg/m^2	380 380	NR	Grade 3 & 4 (%) Neutropenia Fatigue Rash Diarrhea Nausea Vomiting	Erlotinib 42 (12) 51 (13) 40 (11) 20 (5) 12 (3) 13 (3)	C+G 79 (21) 57 (16) 26 (7) 1 (<1) 15 (4) 15 (4)
Crino 2008 INVITE (56) phase 2	Gefitinib 250 mg/day Vinorelbine 30mg/m^2	97 99	24.3% FACT-L 22.9% TOI 42.9% LCS	Grade 3-5 (%) Diarrhea Rash	G 4(4) 2(2)	V 4(4) 0

Reference	Treatment	Number enrolled/ analyzed	Symptom control/Quality of Life	Adverse effects
			36.6% PSI 10.9% FACT-L 6.3% TOI 39.1% LCS 31.0% PSI	Nausea 0 3(3) Vomiting 0 2(2) Constipation 0 2(2) Dyspnea 1(1) 4(4) Fatigue 0 7(7) Neutropenia 0 19(19) Leukopenia 0 7(7) Febrile neutropenia 0 7(7)
Lilenbaum 2008(70) phase 2	Erlotinib 150mg/day Carboplatin AUC6 + Paclitaxel 200mg/m^2	52 51	NR	Grade 3-5 (%) E C+P Rash 4(8) 0 Diarrhea 3(6) 0 Nausea/vomiting 2(4) 2(4) Fatigue 2(4) 5(10) Peripheral neuropathy 0 2(4) Anemia 1(2) 2(4)
Agarwal 2010 (abstr) (90) phase 2	Gefitinib 250 mg/day Carboplatin AUC 5 + Gemcitabine 1000 mg/m^2	18 17	No major differences in QOL	Both G and CG were generally well tolerated.
Morere IFCT-0301 2010 (73) phase 2	Gefitinib 250 mg/day Gemcitabine 1250 mg/m^2 Docetaxel 75mg/m^2	43/43 42/41 42/41	NR	Grades 3 & 4 (%) Gef Gem Doc Rash 1(2) 0 2(4) Diarrhea 2(5) 0 1(2) Nausea/ vomiting 2(4) 0 0 Fatigue 1(2) 2(4) 2(5) Neutropenia 2(5) 4(10) 13(32)
Reck 2010 (Abstr) (99) phase 2	Erlotinib 150mg/day Carboplatin AUC 5 + Vinorelbine 25 mg/m^2	144 140	NR	More skin toxicity and diarrhea was observed by E compared to more myelotoxicity, neurotoxicity and obstipation with CV. Less severe adverse events were observed with E (81 vs. 102)
LeCaer 2011 GFPC 0504 study (68) phase 2	Erlotinib 150mg/day Docetaxel 30 mg/m^2 and Gemcitabine 900 mg/m^2 Reverse on relapse	51 48	NR	Grade 3 & 4 (%) Erlotinib 1st line/2nd line D+G 1st line/2nd line Neutropenia 0/4(16.6) 15(31.3)/0 Diarrhea 2(4)/0 1(2.1)/0 Nausea 0/0 0/0
Chen 2012(53) phase 2	Erlotinib 150mg/day Vinorelbine 60mg/m^2	57 56	FACT-L subscales showed no significant change at the end of treatment for both treatment groups except that patients in the Erlotinib arm had significantly better physical well-being.	Erlotinib – rash (64.9%), diarrhea (29.82%), mouth ulceration (14.04%) Vinorelbine – decreased appetite (26.32%), diarrhea (12.28%), vomiting (10.53%), anorexia (10.53%)

Abbreviations: FACT-L = functional assessment of cancer therapy – lung; LCS = lung cancer subscale; PSI = pulmonary symptom improvement; TOI = trial outcome index.

Table 3. First-line EGFR inhibitor plus chemotherapy vs chemotherapy in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Giaccone 2004 INTACT I (38) phase 3	No prior CT, stage III or IV NSCLC not curable by surgery or radiotherapy, PS 0-2, stable brain Metastases allowed	365/365 365 / 365 363 / 363	Gefitinib 500 mg/day + Gemcitabine 1250 mg/m^2 + Cisplatin 80 mg/m^2 Gefitinib 250 mg/day + above chemotherapy regimen Placebo + above chemotherapy regimen	50.3% (166/330) 51.2% (172/336) 47.2% (153/324)	TTP 5.5 months 5.8 months 6.0 months p=0.7633	9.9 months / 43% 9.9 months / 41% 10.9 months / 44% p=0.456 log rank
Herbst 2004 INTACT 2 (22) phase 3	No prior CT, inoperable stage III or IV NSCLC, PS 0-2, previously treated stable brain metastases allowed	347 / 347 345 / 345 345 / 345	Gefitinib 500 mg/day + Paclitaxel 225 mg/m^2 + Carboplatin AUC 6, Gefitinib 250 mg/day + above chemotherapy regimen Placebo + above chemotherapy regimen	30.0% 30.4% 28.7%	4.6 months 5.3 months 5.0 months	1 year 8.7 months / 37% 9.8 months / 41% 9.9 months 42% p=0.6385
Herbst 2005 TRIBUTE (23) phase 3	No prior CT, stage IIIB or IV NSCLC, PS 0-1	539 540	Paclitaxel 200 mg m^2+ Carboplatin AUC 6 + Erlotinib 150 mg/day Paclitaxel 200 mg m^2+ Carboplatin AUC 6 + placebo	21.5% 19.3% p=0.36	Median TTP 5.1 months 4.9 months p=0.36	10.6 months / 46.9% 10.5 months / 43.8% HR 0.995; 95% CI 0.86-1.16, p=0.95
Gatzemeier , 2007 Tarceva Lung Investigation Trial TALENT (19) phase 3	Unresectable advanced, recurrent or metastatic stage IIIB/IV NSCLC No prior chemotherapy PS 0 or 1	580 579	Erlotinib 150mg/day + Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2 Placebo + Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2	31.5% 29.9%	TTP 23.7 weeks TTP 24.6 weeks HR 0.98; 95% CI 0.86-1.11, p=0.74	43 weeks One-year survival 41% 44.1 weeks One-year survival 42% HR 1.06; 95% CI 0.90-1.23, p=0.49
Mok 2012 FASTACT-II (abstr) (48) phase 3	Untreated IIIB/IV NSCLC PS 0-1	226 225	Gemcitabine 1250 mg/m^2 + Carboplatin 5xAUC or Cisplatin 75 mg/m^2 with intercalculated Erlotinib 150mg/day on days 15-28 Above chemotherapy regimen + Placebo	42.9% 17.8%	7.6 months 6 months HR 0.57; 95% CI 0.46-0.70, p<0.0001	18.3 months 14.9 months HR 0.78; 95% CI 0.60-1.02, p=0.069

Nokikara 2008 (abstr) (98) phase 2	NSCLC Chemo-naïve Stage IIIB of IV PS 0-1	49 48	Carboplatin AUC 6 + Paclitaxel 200mg/m^2 + Gefitinib 250 mg/day Gefitinib 250 mg/day until disease progression followed by Carboplatin AUC 6 + Paclitaxel 200mg/m^2	NR	NR	18.8 months 1 year 61.2% 17.2 months 1 year 68.1%
Mok 2009 (72) phase 2	Stage IIIB or IV NSCLC PS 0 or 1 No prior chemotherapy	76 78	Erlotinib 150mg/day + Gemcitabine 1,250mg/m^2 and either Cisplatin 75mg/m^2 or Carboplatin AUC 5 Placebo + Gemcitabine 1,250mg/m^2 and either Cisplatin 75mg/m^2 or Carboplatin AUC 5	35.5% 24.4%	29.4 weeks 23.4 weeks HR 0.47; 95% CI 0.33-0.6, p=0.0002	74.1 weeks 75.7 weeks HR 1.09; 95% CI 0.70-1.69, log rank p=0.42
Riely 2009 (77) phase 2	Stage IIIB or IV NSCLC No prior chemotherapy and to radiation for 3 weeks. Karnofsky performance status ≥70% Current or former smokers	28 29 29	Erlotinib 150mg/day on days 1 and 2 followed by Carboplatin AUC6 + Paclitaxel 200mg/m^2 on day 3 Erlotinib 1500 mg/day on days 1 and 2 followed by Carboplatin AUC 6 + Paclitaxel 200mg/m^2 on day 3 Carboplatin AUC 6 + Paclitaxel 200mg/m^2 on day 1 followed by Erlotinib 1500 mg/day on days 2 and 3	18% (95% CI 6-37) 34% (95% CI 18-54) 28% (95% CI 13-47)	TTP 4 months (95% CI 3-5) TTP 4 months (95% CI 3-6) TTP 5 months (95% CI 3-8)	10 months (95% CI 8-16) 1-year survival 49% 2-year survival 25% 15 months (95% CI 8-not reached) 1-year survival 63% 2-year survival 42% 10 months (95% CI 5-16) 1 year survival 48% 2 Year survival 26%

Table 4. Adverse effects for first-line EGFR inhibitor plus chemotherapy vs chemotherapy in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Adverse effects
Giaccone 2004 INTACT I (38) phase 3	363 / 363 365 / 365 365 / 365	Gefitinib 500 mg/day + Gemcitabine 1250 mg/m^2 + Cisplatin 80 mg/m^2 Gefitinib 250 mg/day + above chemotherapy regimen Placebo + above chemotherapy regimen	Grades 3 & 4 (%) G 500mg G 250 mg Placebo Rash 12.6 3.6 1.1 Diarrhea 12.0 3.6 2.3 Nausea 4.5 2.5 2.0 Vomiting 4.7 2.8 2.3 Thrombocytopenia 4.2 5.8 5.6 Neutropenia 5.0 5.8 4.8 Pruritus 2.0 0 0
Herbst 2004 INTACT 2 (22) phase 3	345 / 345 345 / 345 347 / 347	Gefitinib 500 mg/day + Paclitaxel 225 mg/m^2 + Carboplatin AUC 6, Gefitinib 250 mg/day + above chemotherapy regimen Placebo + above chemotherapy regimen	Grades 3 & 4 (%) G 500mg G 250 mg Placebo Rash 11.7 3.2 1.5 Diarrhea 25.4 9.9 2.9 Nausea 4.1 1.8 2.1 Vomiting 2.9 2.0 2.3 Neutropenia 6.1 6.7 5.9 Pruritus 1.8 0.6 0.3
Herbst 2005 TRIBUTE (23) phase 3	539 540	Paclitaxel 200 mg m^2 + Carboplatin AUC 6 + Erlotinib 150 mg/day Paclitaxel 200 mg m^2+ Carboplatin AUC 6 + placebo	Except for rash and diarrhea, comparable rates of adverse events in each treatment group. Fatal serious events were more common in Erlotinib group (53 vs. 27), although only 5 of the 80 events were considered Erlotinib-related
Gatzemeier 2007 Tarceva Lung Investigation Trial (19) phase 3	580 579	Erlotinib 150mg/day + Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2 Placebo + Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2	Grades 3 & 4 (%) E P Neutropenia 107(18) 118(20) Anemia 102(18) 73(13) Thrombocytopenia 90(16) 80(14) Leucopenia 54(9) 59(10) Rash 60(10) 4(<1) Dyspnea 40(7) 51(9) Vomiting 39(7) 43(7) Nausea 32(6) 32(6) Diarrhea 35(6) 5(<1) Fatigue 31(5) 30(5)
Mok 2012 FASTACT-II (abstr) (48) phase 3	226 225	Gemcitabine 1250 mg/m^2 plus Carboplatin 5xAUC or Cisplatin 75 mg/m^2 with intercalated Erlotinib 150mg/day Above chemotherapy regimen + Placebo	Except for skin rash with Erlotinib no difference in toxicity between arms
Mok 2009 (72) phase 2	76 78	Erlotinib 150mg/day + Gemcitabine 1250mg/m^2 and either Cisplatin 75mg/m^2 or Carboplatin AUC 5 Placebo + Gemcitabine 1250mg/m^2 and either Cisplatin 75mg/m^2 or Carboplatin AUC 5	Grades 3 & 4 (%) E P Rash 2(3) 0 Nausea 2(3) 0 Fatigue 0 1 Vomiting 2(3) 5(6) Dry Skin 1(1) 0 Pruritus 0 0 Anemia 5(7) 5(6) Neutropenia 10(14) 8(10) Thrombocytopenia 4(5) 4(5)
Riely 2009 (77) phase 2	28 29 29	Erlotinib 150mg/day followed by Carboplatin AUC 6 + paclitaxel 200mg/m^2 and Carboplatin Erlotinib 1500 mg/day 2 followed by Carboplatin AUC 6 + Paclitaxel 200mg/m^2 and Carboplatin Carboplatin AUC 6 + Paclitaxel 200mg/m^2 and Carboplatin followed by Erlotinib 1500 mg/day	Grades 3 & 4 E E+chemo Chemo+E Neutropenia 9 15 11 Anemia 2 0 2 Thrombocytopenia 2 2 0 Neuropathy 1 3 1 Thrombosis 3 2 2 Fatigue 3 3 4 Dyspnea 3 2 2

Other First-Line Trials

Six additional trials were identified (Table 5). Two evaluated an EGFR TKI plus best supportive care vs placebo (42,59). One trial compared erlotinib alone, chemotherapy followed by erlotinib and chemotherapy combined with erlotinib (80), and two compared an EGFR inhibitor to another targeted agent (60,102). The final trial compared chemotherapy, vs chemotherapy plus erlotinib, vs chemotherapy plus bevacizumab and chemotherapy plus erlotinib plus bevacizumab (39). In two trials evaluating an EGFR TKI vs placebo in patients not suitable for chemotherapy, there were no clear differences in PFS or overall survival. Statistical significance was reached in the trial by Lee et al for PFS, but neither showed a difference in overall survival (42,59). Quality of life in the Goss et al trial showed no differences between the two arms (59). For gefitinib, the quality of life improvement rates were: 21.1% - functional assessment of cancer therapy – lung (FACT-L), 18.8% - trial outcome index (TOI), 32.9% - lung cancer subscale (LCS), 28.3% - pulmonary symptom improvement (PSI); and for placebo: 20% - FACT-L, 13.8% - TOI, 30.89% - LCS, and 28.3% - PSI.

In the trial by Stinchcombe at al, both chemotherapy arms had higher response rates and longer PFS, although the differences were not statistically significant. The longest overall survival was observed in patients receiving sequential chemotherapy followed by erlotinib. There was no clear difference in quality of life; Trial Outcome Index (p=0.76), Lung Cancer Subscale (p=0.85) and Functional Assessment of Cancer Therapy - Lung (p=0.57) (80).

The two trials that compared an EGFR inhibitor plus a targeted agent against a targeted agent and chemotherapy showed mixed results. One trial showed that the EGFR inhibitor plus the targeted agent was more effective (60), and the other trial showed the opposite (102).

The trial by Boutsikou had four treatment arms (39). The response rate was the highest in the chemotherapy plus erlotinib arm. Time to progression was significant and the longest in the combination arm p=0.001. Overall survival did not differ between groups.

Table 6 shows the adverse events for first-line EGFR inhibitor with or without chemotherapy versus EGFR inhibitor in unselected patients.

Table 5. First-line EGFR inhibitor with or without chemotherapy vs EGFR inhibitor or placebo in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Lee SM 2014 TOPICAL (42) phase 3	PS 2-3 unfit for platinum chemotherapy because of poor PS Stage IIIB/IV NSCLC Chemo-naive	350 320	Erlotinib 150 mg/day + BSC Placebo + BSC	NR	2.8 months 2.6 months HR 0.83; 95% CI 0.71-0.97, p = 0.019	3.7 months 3.6 months HR 0.94; 95% CI 0.81-1.10, p = 0.46
Goss 2009 (59) phase 2	Stage IIIB/IV NSCLC; PS 2 or 3; No prior EGFR therapy and unfit for chemotherapy; Not amenable to surgery or RT	100 101	Gefitinib 250 mg/day + BSC Placebo + BSC	6.0% 1.0%	43 days 41days HR 0.82; 95% CI 0.60-1.12, p=0.217	3.7 months 2.8 months HR 0.84; 95% CI 0.62-1.15, p=0.272
Stinchcombe 2011 (80) phase 2	Stage IIIB or IV NCSLC PS 0-2 No treatment for metastatic NSCLC and no chemo for over a year Age ≥70	44 51 51	Gemcitabine 1200 mg/m^2 After disease progression, patients offered Erlotinib 150mg/day Erlotinib 150mg/day Erlotinib 100mg/day + Gemcitabine 1000 mg/m^2	7% 0% 21%	3.7 months 95% CI 2.3-4.7 6 months - 22 months 95% CI 11-35 2.8 months 95% CI 1.4-3.4 6 mo - 24 months 95% CI 13-36 4.1 months 95% CI 2.4-5.0 6 mo - 25 months 95% CI 15-38	6.8 months 95% CI, 4.8-8.5 5.8 months 95% CI, 3.0-8.3 5.6 months 95% CI, 3.5-8.4
Gridelli 2011(60) phase 2	NSCLC stage IIIB or IV with pleural effusion or supraclavicular nodes PS 0-2 No prior chemotherapy	29 31	Sorafenib 800 mg/day + Erlotinib 150mg/day Sorafenib 800 mg/day + Gemcitabine 1200 mg/m^2	10.3% 95% CI 2.2-27.4 6.5%; 95% CI 0.8%-21.4	TTP 12.7 wks 95% CI 2.0-69.4 TTP 8.1 weeks 95% CI 1.0-65.0	12.6 months 1 year 51.9% 95% CI 36.0-74.8% 6.55 months 1 year 35.2% 95% CI 21.4-57.7%
Thomas 2011 (Abstr)(102) phase 2	Stage IIIB/IV NSCLC	111 113	Erlotinib 150mg/day + Bevacizumab 15 mg/kg day Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2 + Bevacizumab 15 mg/kg day	12.6% 33.6%	3.7 months 95% CI 2.8-4.3% 7.2 months 95% CI 6.0-8.9%	12.6 months 95% CI 10.3-16.2% 15.7 months 95% CI 11.9-21.7

Boutsikou E 2013 (39) Phase 3	IIIB/IV NSCLC No previous treatment PS 0-1	61	Docetaxel 100 mg/m^2 + carboplatin AUC 5.5	11%	TTP 2.23 month	15.3 months
		52	Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 + Erlotinib 150 mg/day	27%	6.0 months	16.4 months
		56	Bevacizumab 7.5 mg/kg + Docetaxel 100 mg/m^2 + carboplatin AUC 5.5	23%	6.0 months	19.1 months
		60	Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 + Erlotinib 150 mg/day + Bevacizumab 7.5 mg/kg	20%	7.3 months Significant for combination=0.001	22.1 months Did not differ between 4 groups p=0.381

Abbreviations: BSC = best supportive care; RT = radiotherapy

Table 6. Adverse events for first-line EGFR inhibitor with or without chemotherapy versus EGFR inhibitor in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Adverse effects
Lee SM 2014 TOPICAL (42) phase 3	350 320	Erlotinib 150 mg/day + BSC Placebo + BSC	Increased Grade 3/4 rash and diarrhea were observed in Erlotinib group
Boutsikou E 2013 (39) Phase 3	61 52 56 60	Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 + Erlotinib 150 mg/day Bevacizumab 7.5 mg/kg + Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 Docetaxel 100 mg/m^2 + carboplatin AUC 5.5 + Erlotinib 150 mg/day + Bevacizumab 7.5 mg/kg	Grade 3&4 N: CT / CT+E / CT+B / CT+E+B Anemia 4 / 1 / 1 / 4 Neutropenia 6 / 1 / 2 / 2 Thrombocytopenia 0 / 0 / 3 / 2 Rash 0 / 5 / 0 / 8 Diarrhea 0 / 2 / 0 / 4
Stinchcombe 2011 (80) phase 2	44 51 51	Gemcitabine 1200 mg/m^2 After disease progression patients offered Erlotinib 150mg/day Erlotinib 150mg/day Erlotinib 100mg/day + Gemcitabine 1000 mg/m^2 day	Grade ≥3: G / E / E+G Anemia 1(2) / 0 / 4(8) Neutropenia 4(9) / 1(2) / 1(2) Thrombocytopenia 3(7) / 1(2) / 2(4) Diarrhea 0 / 3(6) / 3(6) Dyspnea 2(5) / 0 / 3(6) Fatigue 4(9) / 1(2) / 5(10) Rash 1(2) / 2(4) / 3(6)
Goss 2009 (59) phase 2	100 101	Gefitinib 250mg/day + BSC Placebo + BSC	Grades 3-5 (%): G+BSC / BSC Diarrhea 3(3) / 3(3) Rash 0 / 0 Vomiting 0 / 0 Dyspnea 11(11) / 6(6) Constipation 1(1) / 1(1_ Fatigue 6(6) / 8(8) Pruritus 0 / 0 Anemia 3(3) / 0
Gridelli 2011 (60) phase 2	29 31	Sorafenib 800 mg/day + Erlotinib 150mg/day Sorafenib 800 mg/day + Gemcitabine 1200 mg/m^2/day	Grades 3-4 (%): S+E / S+gem Anemia 1(3) / 0 Neutropenia 0 / 1(3) Thrombocytopenia 1(3) / 1(3) Fatigue 4(14) / 4(13) Skin rash 4(14) / 0 Paronchia 0 / 0 Diarrhea 5(17) / 1(3) Nausea 0 / 0 Vomiting 0 / 0
Thomas 2011 (abstr)(102) phase 2	111 113	Erlotinib 150mg/day + Bevacizumab 15 mg/kg/ day Gemcitabine 1250 mg/m^2 and Cisplatin 80 mg/m^2 + Bevacizumab 15 mg/kg/day	E+B / CG+B Hematologic grade 3: 6.5% / 27.3% Hematologic grade 4: 0.9% / 27.3% Non-hematologic grade 3: 34.3% / 34.6% Non-hematologic grade 4: 9.3% / 24.6%

First-line Clinically Selected Population

Eight trials identified the use of an EGFR inhibitor in stage IIIB/IV NSCLC patients selected using clinical characteristics thought to predict response to an EGFR TKI (Asian ethnicity, female gender, age, adenocarcinoma histology, and light or never smokers; Table 7). There are four fully published trials (21,30,64,69) and four abstracts (97,104,105,107). One abstract was an update to a fully published trial (107).

First-line EGFR Inhibitor in Clinically Selected Patients

Four studies were identified that evaluated an EGFR inhibitor against chemotherapy in clinically selected patients in the first-line setting. Three of the trials found a greater response rate in the EGFR inhibitor group than in the chemotherapy group (21,30,69). The results were significant in the IPASS study ($p<0.001$) (30).

There was an increase in PFS in the Liang et al and IPASS trials (30,97). The results were statistically significant in the IPASS trial ($p<0.001$) (30). The First Signal trial showed a decrease in PFS for the EGFR inhibitor group, although this result was not statistically significant (21). The GFPC 505 study by LeCaer et al showed no statistical difference in time to progression ($p=0.58$) in the first-line setting (69). Overall survival showed no difference between the groups in all four trials (21,69,97,107).

Subgroup analyses for the IPASS and First Signal trials were done in patients with tumour samples available for EGFR mutation testing (21,30). In the First Signal trial, EGFR mutation-positive patients who were treated with gefitinib compared to the gemcitabine and cisplatin showed a higher overall response rate (84.6% vs 37.5%, $p=0.002$) and a trend toward longer PFS (HR 0.544; 95% CI 0.269-1.100, $p=0.086$). In the mutation-negative subgroup, the gemcitabine and cisplatin arm, compared to the gefitinib arm, showed a trend toward higher overall response rate (51.9% vs 25.9%, $p=0.051$) and longer PFS (HR 1.419; 95% CI 0.817-2.466, $p=0.226$). For overall survival, there were no significant differences between both treatment arms according to EGFR mutation status. The HRs for gefitinib versus gemcitabine and cisplatin were 1.043 (95% CI 0.498-2.182) in the mutation-positive subgroup, 1.000 (95% CI 0.523-1.911) in the mutation-negative subgroup, and 0.880 (95% CI 0.639-1.210) in the mutation-unknown subgroup (21).

In the IPASS trial, there was evidence of an interaction between treatment arms and EGFR mutation status. PFS was significantly longer for patients receiving gefitinib than for those receiving carboplatin–paclitaxel in the mutation-positive subgroup (HR 0.48; 95% CI 0.36-0.64, $p<0.001$). PFS was significantly shorter in patients receiving gefitinib than in those receiving carboplatin–paclitaxel in the mutation-negative subgroup (HR 2.85; 95% CI 2.05-3.98, $p<0.001$). Results in the subgroup with unknown EGFR-mutation status were similar to those for the overall population. Overall survival also showed a trend towards longer survival with gefitinib in the mutation-positive subgroup (HR 0.78; 95% CI 0.50-1.20) than in the mutation-negative subgroup (HR 1.38; 95% CI 0.92-2.09) and in the mutation-unknown subgroup (HR 0.86; 95% CI 0.68-1.09) (30). These results suggest that the benefit of first-line therapy with an EGFR TKI is limited to patients with tumours known to harbour an EGFR mutation.

One trial evaluated the combination of an EGFR TKI plus chemotherapy versus an EGFR TKI in clinically selected patients. The response rate was greater in the EGFR plus chemotherapy arm, as was the median PFS, although this result was not significant ($p=0.1988$) (64). However, overall survival was higher in the EGFR inhibitor-alone group. Adverse effects were consistent with those associated with chemotherapy and EGFR inhibitors (64).

Two additional trials evaluated the combination of an EGFR TKI plus chemotherapy versus chemotherapy in clinically selected patients. The response rate was greater in the chemotherapy plus erlotinib arm in the Choi study (104) and greater in the chemotherapy only arm for the Michael study (105). The median PFS was higher in the combination arm in the Michael trial and showed no difference in the Choi trial. These results were not significant in either group (104,105). Overall survival was higher in the chemotherapy group in the Choi trial and not reported in the Michael trial (104,105).

Table 7. First-line EGFR inhibitor Vs chemotherapy in selected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Mok 2009 IPASS (30) Yang 2010 IPASS OS update (abstr)(107) phase 3	Stage IIIB/IV NSCLC with adenocarcinoma features; Non- or former light smokers; No prior therapy; PS 0-2	609 608	Gefitinib 250 mg/day Paclitaxel 200 mg/m^2 + Carboplatin AUC 5 or 6	43% 32.2% OR 1.59; 95% CI,1.25-2.01; p<0.001	5.7 months 12 months 24.9% 5.8 months 12 months 6.7% HR 0.74; 95% CI 0.65-0.85, p<0.001	18.8 months 17.4 months HR 0.901; 95% CI 0.793-1.023, p=0.109
Han 2012 First-SIGNAL (21) phase 3	IIIB/IV NSCLC Never smokers Chemo-naive PS 0-2	159 154	Gefitinib 250 mg/day Gemcitabine 1250 mg/m^2 + Cisplatin 75 mg/m^2	55.4% 46.0%	5.8 months 6.4 months HR 1.198; 95% CI 0.944-1.520, p=0.138	22.3 months 22.9 months HR 0.932; 95% CI 0.716-1.213, p=0.604
Liang 2010 (abstr) (97) phase 2	NSCLC Never smoker Chemo-naive Stage IIIB/IV PS ≤1	25 24	Pemetrexed 500mg/ m^2 + Visplatin 75/mg/m^2 + Gefitinib 250mg/day Pemetrexed 500mg/ m^2 + Cisplatin 75/mg/m^2	NR	9.95 months 6.83 months HR 0.533; 95% CI 0.272-1.044, p=0.067	12 months 74.8% 24 months 59.6% 12 months 93.3% 24 months 71.1%
LeCaer 2012 GFPC 0505 (69) phase 2	IIIB/IV NSCLC Combined age, PS and Charleton score of vulnerable elderly patients No prior chemotherapy	50 44	Erlotinib 150 mg/day Gemcitabine 1250 mg/m^2 Reverse on relapse	1st line 12% 2nd line 8% 1st line 11.4% 2nd line 4.5%	TTP1 2.2 months TTP2 3.5 months TTP1 2.5 months TTP2 4.3 months TTP1 p=0.58 TTP2 p=0.55	3.9 months 4.4 months p=0.26
Janne 2012 CALGB 30406 (64) phase 2	IIIB/IV NSCLC Chemo-naive Light or never smokers > 100 cigarettes and ≤10 pack years and quit ≥ 1 year ago PS 0-1	81 100	Erlotinib 150 mg/day Erlotinib 150 mg/day + Paclitaxel 200 mg/m^2 + Carboplatin (AUC 6)	35% 46%	5.0 months 95% CI 2.9-7.0 6.6 months 95% CI 5.4-8.2, p=0.1988	24.6 months 95% CI 18.4-33.8 19.8 months 95% CI 14.4-27.8

Choi YJ 2013 abstr (104) phase 2	Advanced NSCLC Smokers or wild type Chemo-naive	44 46	Gefitinib 250 mg/day (day 2 to 15 of 3 week cycle)+ Paclitaxel 175 mg/m^2 + Carboplatin AUC 5 Paclitaxel 175 mg/m^2 + Carboplatin AUC 5	40.9% 37.0%	4.13 months 4.13 months HR 0.941; 95% CI 0.61-1.45, p=0.781	9.33 10.53 HR 0.95; 95% CI 0.58-1.54, p=0.827
Michael M GATE 2012 abstr (105) phase 2	Elderly or PS 2 Advanced NSCLC Chemo-naive	26 28	Erlotinib 150mg/day (days 15-28) + Gemcitabine 1000 mg/m^2 Gemcitabine 1000 mg/m^2	3.8% 7.1%	10.3 months 8.0 months HR 1.3; 95% CI 0.63-2.68, p=0.4798	NR

OR = Odds ratio.

Results for symptom control and quality of life were addressed in two studies (Table 8). The IPASS trial saw statistical and clinically relevant improvement in quality of life with the use of the EGFR inhibitor (30). The First-SIGNAL trial found significant differences in physical ($p<0.001$) and social functions ($p=0.013$) in favour of gefitinib. There were no significant differences between emotional and cognitive functions (21).

Adverse effects were consistent with those known for EGFR inhibitors and chemotherapy.

Table 8. Symptom control and quality of life in first-line EGFR inhibitor versus chemotherapy in selected patients.

Reference	Treatment	Number enrolled	Symptom control/Quality of life	Adverse effects		
Mok 2009 IPASS (30) Yang 2010 IPASS OS update (abstr)(107) phase 3	Gefitinib 250mg/day Paclitaxel 200 mg/m^2 + Carboplatin AUC 5 or 6	609 608	More patients in the Gefitinib group had clinically relevant improvement in QoL FACT-L (OR 1.34; 95%CI 1.06-1.69, p=0.01); TOI (OR 1.78; 95%CI 1.40-.26, p<0.001)	Grades 3-5 (%) Rash or acne Diarrhea Pruritus Nausea Paronychia Vomiting Constipation Neutropenia Anemia	G 19(3.1) 23(3.8) 4(0.7) 2(0.3) 2(0.3) 1(0.2) 0 22(3.7) 13(2.2)	P+C 5(0.8) 8(1.4) 1(0.2) 9(1.5) 0 16(2.7) 1(0.2) 387(67.1) 61(10.6)
Han 2012 First-SIGNAL (21) phase 3	Gefitinib 250mg/day Gemcitabine 1250 mg/m^2 + Cisplatin 75 mg/m^2	159 154	According to the European Organization for research and treatment of cancer quality of life questionnaire significant differences in favour of Gefitinib were found in physical functioning (p<0.001)and social functioning (p=0.013)	Grade 3 & 4 (%) Rash Diarrhea Pruritus Fatigue Nausea Vomiting Neutropenia	Gefitinib 47 (29.3) 4(2.5) 0 16(10) 0 0 3(1.9)	G+C 3(2) 2(1.3) 0 68(45.3) 4(2.6) 11(7.3) 82(54.6)
Liang 2010 (abstr) (97) phase 2	Pemetrexed 500mg/ m^2 + Cisplatin 75/mg/m^2 + Gefitinib 250mg/day Pemetrexed 500mg/ m^2 + Cisplatin 75/mg/m^2	25 24	NR	No significant difference was observed between tx arms for grade 3/4/5 toxicities.		
LeCaer 2012 GFPC 0505 (69) phase 2	Erlotinib 150 mg/day Gemcitabine 1250 mg/m^2 Reverse on relapse	50 44	NR	Grades 3 & 4 (%) Diarrhea Nausea Vomiting	Erlotinib 1st line / 2nd line 3(6)/0 0/0 0/1(4)	Gemcitabine 1st line/2nd line 0/0 1(2.3)/0 0/0
Janne 2012 CALGB 30406 (64) phase 2	Erlotinib 150 mg/day Erlotinib 150 mg/day + Paclitaxel 200 mg/m^2 + Carboplatin (AUC 6)	81 100	NR	Grade 3&4 (%) Neutropenia Diarrhea Fatigue Nausea Rash Vomiting	E 0 4(5) 1(1) 1(1) 6(7) 1(1)	E+PC 41 7(7) 17(17) 7(7) 10(10) 7(7)

Choi YJ 2013 Abstr phase 2	Gefitinib 250 mg/day (day 2 to 15 of 3 week cycle)+ paclitaxel 175 mg/m^2 + carboplatin AUC 5 paclitaxel 175 mg/m^2 + carboplatin AUC 5	44 46			G Rash 58% diarrhea 14%	chemo 9% 7%

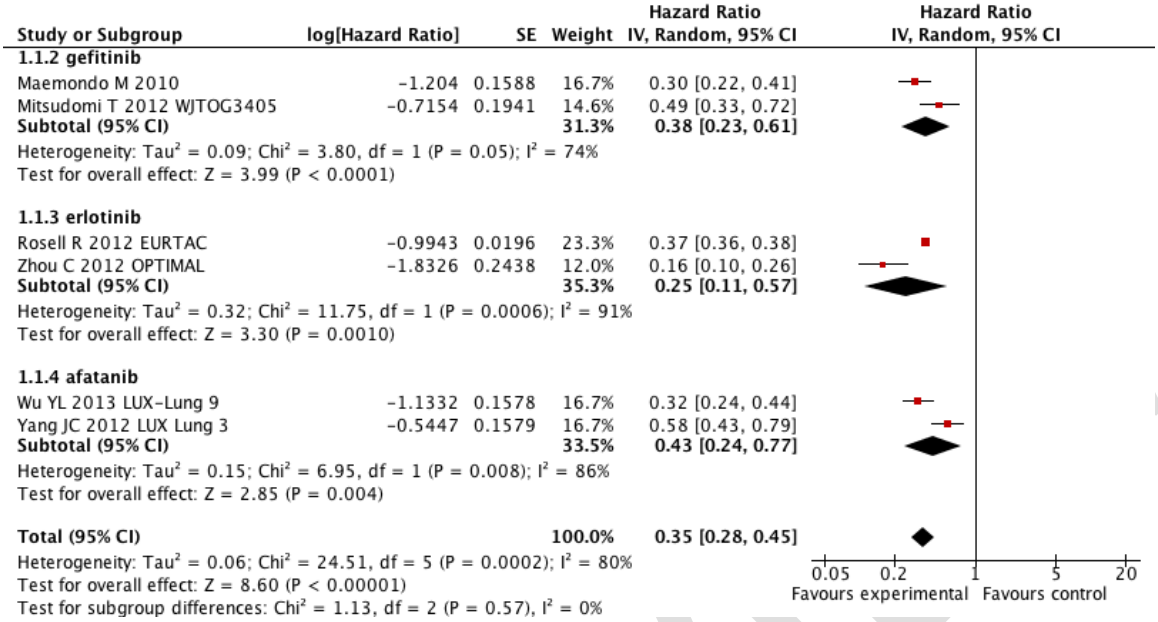
First-line Molecularly Selected Population

Seven trials identified the use of an EGFR inhibitor in molecularly selected patients with stage IIIB/IV NSCLC. Six trials selected patients with tumours harbouring an EGFR mutation. One additional trial selected patients on the basis of EGFR protein overexpression assessed by IHC or increased gene copy number assessed by FISH. These results can be seen in Table 9. There are six fully published trials (27,29,32,36,44,63) and one abstract (50). Six trials compared an EGFR inhibitor against chemotherapy (27,29,32,36,44,50). One trial compared an EGFR inhibitor vs an EGFR inhibitor plus chemotherapy (63). Three additional abstracts provided updated results to published trials (108-110). A meta-analysis was performed in this group of patients because the patients were homogenous, and their comparators were platinum-based chemotherapy regimens.

Six trials were identified that examined the use of an EGFR inhibitor against chemotherapy in patients known to have an EGFR mutation (Table 9). All six trials observed higher response rates in favour of the EGFR inhibitor group. Three of the trials (Mitsudomi et al, Zhou et al and Yang et al) found the results to be statistically significant ($p>0.0001$) (29,36,50).

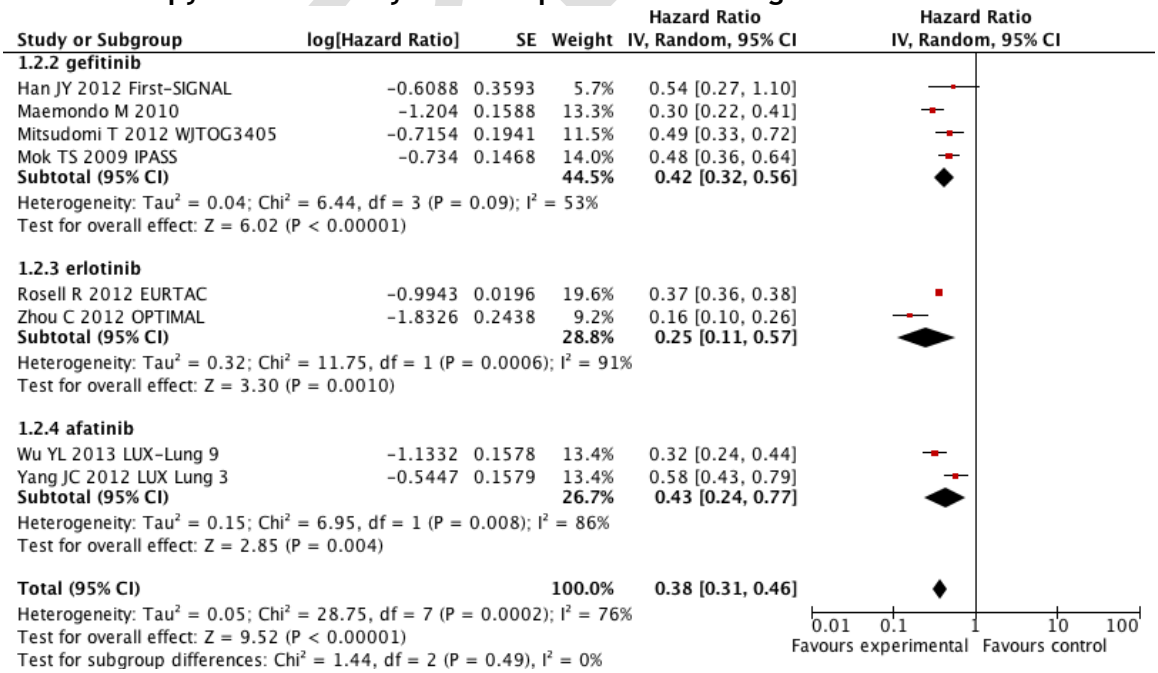
PFS was also statistically significant for every trial and in favour of the EGFR inhibitor (27,29,32,36,44,50). These results, which were pooled in a meta-analysis (Figure 1), were statistically significant (HR 0.35; 95%CI 0.28-0.45, $p<0.00001$). However, the I^2 is high at 80%, which shows considerable statistical heterogeneity. In each of the subgroup analyses with the different EGFR inhibitors, the I^2 also remains high. The cause of the heterogeneity remains unknown at this time.

Figure 1. Meta-analysis of PFS in EGFR inhibitors versus chemotherapy in molecularly selected patients.



The addition of the subgroup analyses from both IPASS and First-Signal trials in patients with known EGFR mutation status (21,30) has little impact on the results of the meta-analysis (HR 0.38; 95% CI 0.31-0.46, p<0.00001) (Figure 2). Evidence of statistical heterogeneity remains an I^2 of 76%.

Figure 2. Meta-analysis of progression-free survival in EGFR inhibitors versus chemotherapy in molecularly selected patients including IPASS and First-SIGNAL trials.



Overall survival was reported in six trials. These data may be difficult to interpret as many patients are likely to have crossed over to the other treatment arm, but the actual percentages are not reported. However, meta-analysis of these trials demonstrates no difference in survival between the two groups (HR 1.01; 95% CI 0.86-1.18; p=0.94) (Figure 3). Inclusion of data from the IPASS and First-Signal trials did not change this result (HR 0.98; 95% CI 0.84-1.14, p=0.77) (Figure 4).

One additional study compared an EGFR inhibitor plus chemotherapy vs an EGFR inhibitor in patients with EGFR protein overexpression or increased gene copy number (63). A higher response rate was observed in the EGFR plus chemotherapy group (22.4%) vs the EGFR-inhibitor group (11.6%). The median PFS was also longer in the EGFR plus chemotherapy group (4.57 months) vs 2.69 months for the EGFR-inhibitor group. However, overall survival was longer in the EGFR-inhibitor group alone (16.7 months) vs 11.43 months in the EGFR-inhibitor plus chemotherapy group. The most significant toxicity was skin rash, which occurred in slightly higher numbers in the EGFR-inhibitor alone group (63).

Figure 3. Meta-analysis of overall survival in EGFR inhibitors vs chemotherapy in molecularly selected patients.

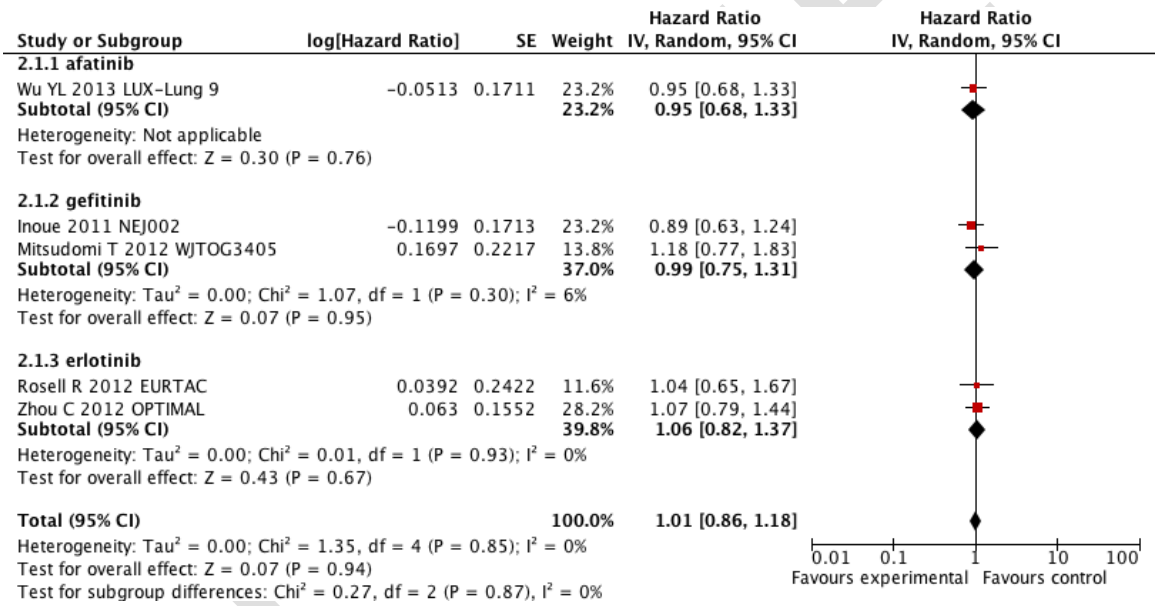
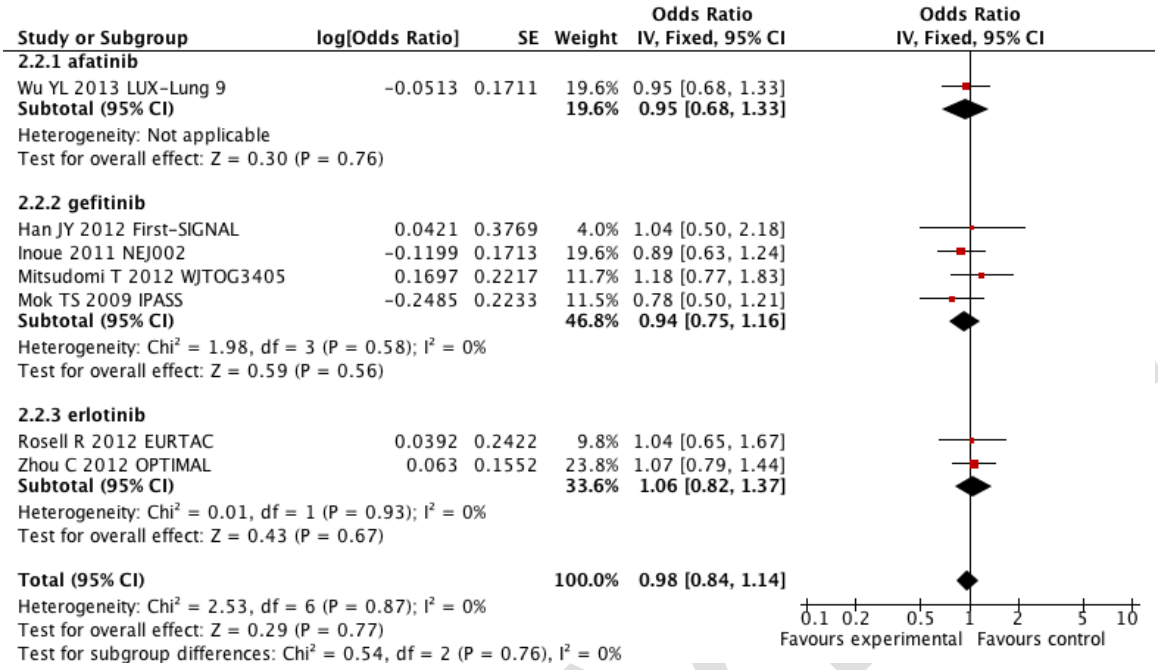


Figure 4. Meta-analysis of overall survival in EGFR inhibitors vs chemotherapy in molecularly selected patients including IPASS and First-SIGNAL trials.



Symptom control and quality of life were discussed in the Yang et al study (50) and the Wu study (44). The results can be seen in Table 10. A significant delay in time to deterioration of cancer-related symptoms of cough (HR 0.60, p=0.0072) and dyspnea (HR 0.68; p=0.0145) was seen with the EGFR inhibitor afatinib (50). A higher proportion of patients in the afatinib group had significantly longer time to deterioration HR 0.56; 95% CI 0.41-0.77, p=0.0002 (44).

The adverse effects were consistent with those found with EGFR inhibitors and chemotherapy.

Table 9. First-line EGFR inhibitor in molecularly selected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate	Median progression-free survival	Median overall survival
Maemondo 2010 NEJ002 (27) Inoue 2011 (110) NEJ002 update (abstr) phase 3	Stage IIIB or IV NSCLC; An EGFR mutation PS 0 or 1 Chemo-naive	115 115	Gefitinib 250mg/day Paclitaxel 200 mg/m^2 + Carboplatin AUC 6	73.7% 30.7% p<0.001	10.8 months 1 & 2 year PFS 42.1% and 8.4% 5.4 months 1 & 2 year PFS 3.2% and 0% HR 0.30; 95% CI 0.22-0.41, p<0.001	27.7 months 2 year 57.9% 26.6 months 2 year 53.7% HR 0.887; 95% CI 0.634-1.241, p=0.483
Mitsudomi 2010 WJTOG3405 (29, 108) phase 3	Stage IIIB or IV; Mutation either exon 19 deletion or L858R in exon 21; PS 0-1; No previous therapy in the last 6 months	86 86	Gefitinib 250mg/day Docetaxel 60mg/m^2 + cisplatin 80/mg/m^2	62.1% 32.2% 95%CI 12.6-74.1%, p<0.0001	9.2 months 95% CI 8.0-13.9 6.3 months 95% CI 5.8-7.8 PFS in favour of Gefitinib HR 0.489; 95% CI 0.336-0.710; p<0.0001	36 months 39 months HR 1.185; 95% CI 0.767-1.829
Zhou 2011 OPTIMAL, CTONG-0802 (36, 109) phase 3	Advanced or recurrent stage IIIB or IV NSCLC Confirmed activating mutation of EGFR in exon 19 or 21. PS 0-2	83 82	Erlotinib 150 mg/day Gemcitabine 1000 mg/m^2 + Carboplatin AUC 5	83% 36% (p<0.0001)	13.1 months 95% CI 10.58-16.53 4.6 months 95% CI 4.21-5.42 HR 0.16; 95% CI 0.10-0.26, p<0.0001	Overall survival did not differ significantly between treatment arms HR 1.065, p=0.6849
Rosell 2012 EURTAC(32) phase 3	IIIB/IV NSCLC No prior chemotherapy for metastatic disease An EGFR mutation	86 87	Erlotinib 150 mg/day Cisplatin 75/mg/m^2 + Docetaxel 75mg/m^2 or Gemcitabine 1250 mg/m^2. *Or* Carboplatin AUC 6 with Docetaxel	54.6% 14.9%	9.7 months 5.2 months HR 0.37; 95% CI 0.25-0.54, p<0.0001	19.3 months 19.5 months HR 1.04; 95% CI 0.65-1.68, p=0.870

			75mg/m^2 or Carboplatin AUC 5 with Gemcitabine 1000 mg/m^2			
Wu Y-L 2013 LUX-Lung 6 (44) Phase 3	Stage IIIB/IV NSCLC PS 0-1 Chemo-naïve EGFR mutation	242 122	Afatinib 40 mg/day Gemcitabine 1000 mg/m^2 + Cisplatin 75 mg/m^2	66.9% 23.0%	11 months 5.6 months HR 0.28; 95% CI 0.20-0.39	22.1 months 22.2 months HR 0.95; 95% CI 0.68-1.33, p=0.76
Yang 2012-10-26 LUX-Lung 3 (abstr)(50) phase 3	Stage IIIB/IV NSCLC PS 0-1 Chemonaive An EGFR mutation	230 115	Afatinib 40 mg/ day Pemetrexed 500 mg/m^2 with Cisplatin 75 mg/m^2	56% 23% p<0.0001	11.1 months 6.9 months HR 0.58; 95% CI 0.43-0.78, p=0.0004	
Hirsch FR 2011(63) phase 2	Stage IIIB or IV newly diagnosed NSCLC who has EGFR positive tumours assessed by IHC or FISH	72/69 71/68	Erlotinib 150 mg/day Erlotinib 150 mg/day + Paclitaxel 200 mg/m^2 + Carboplatin AUC 6	11.6% 22.4%	2.69 months 6-month rate 30.7% 4.57 months 6-month rate 26.4%	16.7 months 1 year 59% 11.43 months 1 year 46%

Table 10. Adverse effects of first-line EGFR inhibitor vs chemotherapy in molecularly selected patients.

Reference	Number enrolled/ analyzed	Treatment	Adverse effects		
Maemondo 2010 (27) phase 3	115 115	Gefitinib 250 mg/day Paclitaxel 200 mg/m^2 + Carboplatin AUC 6	Grades 3 & 4 (%) Diarrhea Fatigue Rash Neutropenia Anemia Thrombocytopenia	G 1(0.9) 3(2.6) 6(5.3) 1(0.9) 0 0	P+C 0 1(0.9) 3(2.7) 74(65.5) 6(5.3) 4(3.5)
Mitsudomi 2010 WJTOG3405 (29, 108) phase 3	86 86	Gefitinib 250 mg/day Docetaxol 60 mg/m^2 + cisplatin 80 mg/m^2	Grade ≥3 Rash Diarrhea Fatigue Paronychia Nausea Constipation Thrombocytopenia Neutropenia Anemia	G 2 1 2 1 1 0 0 0 0	D+C 0 0 2 1 3 0 0 74 15
Zhou 2011 OPTIMAL, CTONG-0802 (36, 51) phase 3	83 82	Erlotinib 150 mg/day Gemcitabine 1000 mg/m^2 + Carboplatin AUC 5	Grade 3 & 4 (%) Neutropenia Thrombocytopenia Anemia Skin rash Diarrhea Paronychia Vomiting or nausea Constipation Fatigue	E 0 0 0 2(2) 1(1) 0 0 0 0	G+C 30(42) 29(40) 9(13) 0 0 0 1(1) 0 1(1)
Rosell 2012 EURTAC(32) phase 3	86 87	Erlotinib 150 mg/day Cisplatin 75 mg/m^2 + Docetaxel 75 mg/m^2 or Gemcitabine 1250 mg/m^2. *Or* Carboplatin AUC 6 with Docetaxel 75 mg/m^2 or Carboplatin AUC 5 with Gemcitabine 1000 mg/m^2	Grade3 & 4 (%) Fatigue Rash Diarrhea Neutropenia Thrombocytopenia	Erlotinib 5(6) 11(13) 4(5) 0 0	Chemo 16(20) 0 0 18(22) 12(14)
Wu Y-L 2013 LUX-Lung 9 (44) Phase 3	242 122	Afatinib 40 mg/day Gemcitabine 1000 mg/m^2 + Cisplatin 75 mg/m^2	Grade3&4 (%) Diarrhea Rash or Acne Pruritus Fatigue Vomiting Anemia Neutropenia Thrombocytopenia	Afatinib 13(5.4) 35 (14.6) 1(0.4) 1(0.4) 2(0.8) 1(0.4) 1(0.4) 1(0.4)	Gem + Cis 0 0 0 1(0.9) 22(19.4) 10(8.8) 30(26.5) 11(9.7)
Yang 2012-10-26 LUX-Lung 3 (abstr)(50) phase 3	230 115	Afatinib 40 mg/day Pemetrexed 500 mg/m^2 with Cisplatin 75 mg/m^2	Afatinib – diarrhea (95%), rash (62%), paronychia (57%) Pemetrexed and cisplatin – nausea (66%), decreased appetite (53%), vomiting (42%)		
Hirsch 2011 (63) phase 2	72/69 71/68	Erlotinib 150 mg/day Erlotinib 150 mg/day + Paclitaxel 200 mg/m^2 + Carboplatin AUC 6	Grade 3 (4) Rash	E 81% (9%)	E+CP 76% (4%)

Second-Line Treatment

Unselected Population

Forty-two studies were identified that compared an EGFR inhibitor with another treatment in an unselected population of patients. Ten studies examined the use of an EGFR inhibitor vs chemotherapy (17,25,26,28,41,47,49,57,65,96). An EGFR inhibitor vs an EGFR inhibitor plus chemotherapy was examined in five studies (54,55,82,92,93). Seventeen studies examined the use of an EGFR inhibitor alone or in combination with a targeted agent (24,31,33,61,62,71,74,76,78,79,81,84,86,89,94,100,101,111). One study examined an EGFR inhibitor plus chemotherapy vs chemotherapy (103), and three studies examined an EGFR inhibitor versus placebo (8,18,37), and five studies examined an EGFR inhibitor versus another EGFR inhibitor (43,58,67,75,91).

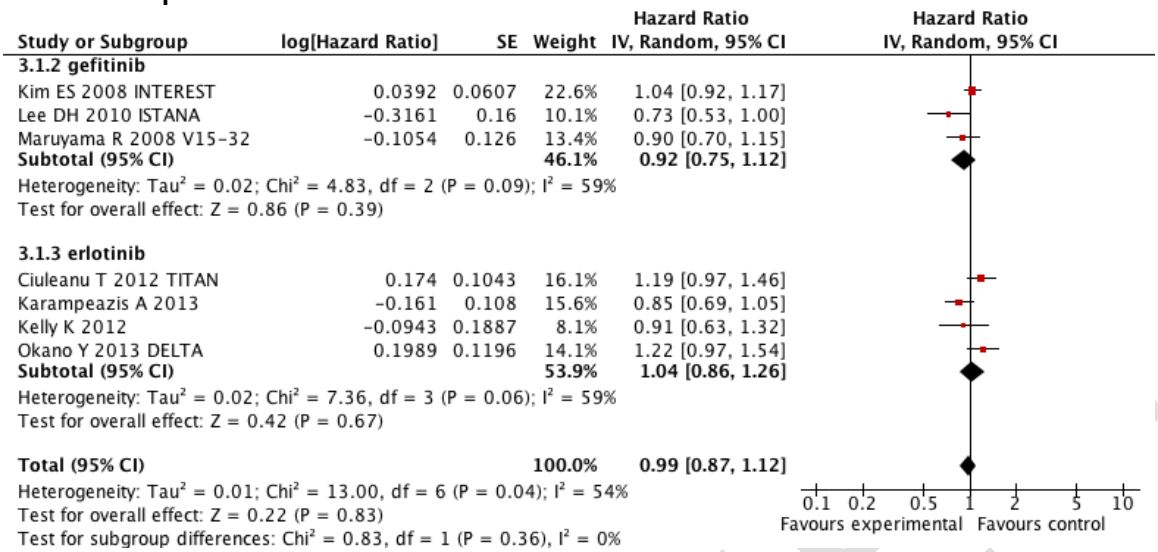
Second-line EGFR Inhibitor vs Chemotherapy in Unselected Patients

Ten studies examined the use of an EGFR inhibitor against chemotherapy in second-line treatment (17,25,26,28,41,47,49,57,65,96) (Table 11). Seven of these were fully published papers (17,25,26,28,41,57,65), and three were abstracts (47,49,96). A meta-analysis was done in this population because of available data and a clinically homogenous population.

No significant difference in response rate was observed in six of the ten studies (17,25,41,49,57,65,96). Four studies, done in Asian populations, showed a significantly higher response rate (25,26,28,65).

PFS was also similar between the groups in all the trials except for the INSTANA study by Lee et al. At the six-month mark, the gefitinib group was at 32% and the docetaxel at 13% (HR 0.729; 90 CI 0.533-0.998, 1-sided p=0.0441) (26). A meta-analysis was performed on seven of the studies in this group (Figure 5). Three of the studies did not provide enough data to be included in the analysis (49,57,96). There was no difference in PFS between EGFR TKIs and chemotherapy (HR 0.99; 95% CI 0.87-1.312, p=0.83). The I^2 in this analysis is still high at 54%, which shows evidence of statistical heterogeneity. Biomarker studies performed in the INTEREST trial demonstrated that EGFR protein expression, gene copy number, mutation status and K-RAS mutation status were not predictive of any difference in overall survival for either gefitinib or docetaxel (112). EGFR mutation status predicted a longer PFS for patients treated with gefitinib (HR 0.16; 95% CI .05-.49, p=0.001). However, the results overall suggest that second-line therapy with an EGFR TKI or with chemotherapy are both reasonable alternatives.

Figure 5. Meta-analysis of EGFR inhibitor vs chemotherapy for PFS in second-line unselected patients.



Similar findings were observed with overall survival. A meta-analysis showed no difference in overall survival for second-line EGFR TKI or chemotherapy (HR 1.02; 95% CI 0.95-1.09; p=0.56) (Figure 6). There did not appear to be significant heterogeneity between trials for overall survival (I^2 0%).

Figure 6. Meta-analysis of EGFR inhibitor vs chemotherapy for overall survival in second line unselected patients.

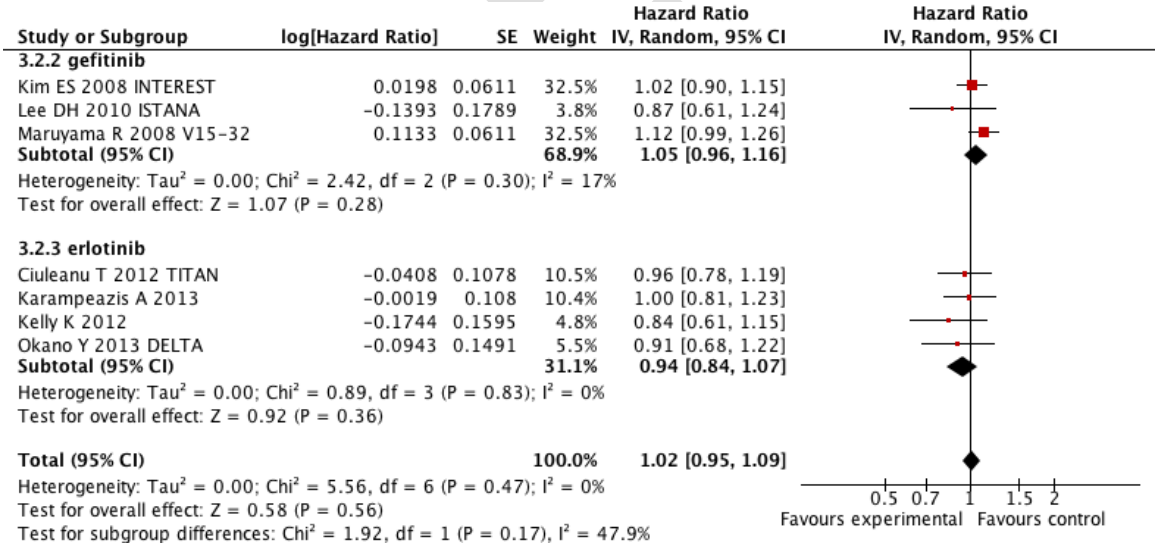


Table 11. Second-line EGFR inhibitor vs chemotherapy in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Kim 2008 INTEREST(25) phase 3	Locally advanced or metastatic NSCLC that has recurred or progressed after 1 or 2 previous platinum-based chemotherapy regimens PS 0-2 No previous EGFR therapy	733 733	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	27.2% 31.1%	2.2 months 6 months 19% 2.7months 6 months 18% HR 1.04; 95% CI 0.93-1.18	7.6 months 1 year 32% 8.0 months 1 year 34% HR 1.020; 96% CI 0.905-1.150
Maruyama 2008 V-15-32 (28) phase 3	Advanced or metastatic stage IIIb or IV NSCLS who failed 1 or 2 platinum-based chemotherapy regimens. Ps 0-2	245/244 244/239	Gefitinib 250 mg/day Docetaxel 60 mg/m^2	22.5% 12.8% (OR 2.14; 95%CI 1.21-3.78, p=0.009)	2 months for both groups HR 0.90; 95% CI 0.72-1.12, p=0.335	1 year 11.5 months and 47.8% 1 year 14.0 months and 53.7% HR 1.12; 95% CI 0.89-1.40; p=0.330
Lee 2010 ISTANA (26) phase 3	Stage IIIB or IV NSCLC One previous platinum-doublet chemotherapy regimen. PS0-2	82 79	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	28.1% 7.6% (p=0.0007)	3.3 months 6 months 32% 3.4 months 6 months 13% HR 0.729; 90% CI 0.533-0.998 1-sided p=0.0441	14.1 months 12.2 months HR 0.870; 95% CI 0.613-1.236, 2-sided p=0.4370
Vamvakas 2010 (abstr)(49) phase 3	Advanced/meta-static NSCLC	147 150	Pemetrexed 500 mg/m^2 Erlotinib 150 mg/day	11.6% 6.8%; (p=0.166)	TTP 2.9 months 3.6 months p=0.434	8.9 months 7.7 months p = 0.528
Ciuleanu 2012 TITAN(17) phase 3	Advanced NSCLC Had disease progression while on SATURN trial PS 0-2	203 221	Erlotinib 150 mg/day Docetaxel or pemetrexed	7.9% 6.3%	6.3 weeks 8.6 weeks HR 1.19; 95% CI 0.97-1.46, p=0.089	5.3 months 5.5 months HR 0.96; 95% CI 0.78-1.19, p=0.73

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
			dose determined by centre			
Karampeazis A 2013 (41) Phase 3	IIIB/IV NSCLC 1 or 2 previous chemotherapy regimens (including platinum for < 65y) PS0-2	179 178	Erlotinib 150 mg/day Pemetrexed 500mg m^2	9.0% 11.4% p=0.469	3.6 months 2.9 months p=0.136	8.2 months 10.1 months p=0.986
Okano Y 2013 DELTA (abstr) (47) Phase 3	IIIB/IV NSCLC Previously treated with 1 or 2 chemo regimens including one platinum agent PS 0-2	150 151	Erlotinib 150mg/day Docetaxel 60mg/m^2	NR	2.0 months 3.2 months p=0.092 HR 1.22; 95% CI 0.97-1.55	14.8 months 12.2 months p=0.527 HR 0.91; 95% CI 0.68-1.22
Cufer 2006 SIGN(57) phase 2	Advanced stage IIIB/IV NSCLC PS 0-2	68 73	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	13.2% 13.7%	3.0 months 3.4 months	7.5 months 6 months 65.6% 7.1 months 6 months 56.1%
Hong 2010 (abstr) (96) phase 2	Pre-treated stage IIIB/IV NSCLC PS 0-2	32 34	Pemetrexed 500 mg/m^2 Gefitinib 250 mg/day	6.3% 11.8% p= 0.74	2.0 months 2.3 months p=0.74	8.1 months 7.9 months (p= 0.60)
Kelly 2012 (65) phase 2	IIIB/IV NSCLC 1-2 prior platinum-based chemotherapy regimens. Lifetime of ≥100 cigarettes PS 0-1	101 100	Erlotinib 150 mg/day Pralatrexate 190 mg/m^2	7% 2%	2.8 months 3.4 months HR 0.91; 95% CI 0.63-1.32	7 months 6.7 months HR 0.84; 95% CI 0.61-1.14

IQR = interquartile range; PR = progressive response.

Symptom improvement and quality of life can be seen in Table 12. Four studies evaluated symptom control and quality of life. All four of the studies found that the use of an EGFR inhibitor improved both symptom control and quality of life (17,26,28,57). Adverse effects were consistent with those associated with EGFR inhibitors and chemotherapy.

Table 12. Symptom control and quality of life in second-line unselected patients treated with an EGFR inhibitor or chemotherapy.

Reference	Number enrolled/ analyzed	Treatment	Quality of life	Adverse effects		
Kim 2008 INTEREST (25) phase 3	733 733	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	NR	Grade 3 & 4 (%) Neutropenia Rash/acne Diarrhea Nausea Dyspnea Vomiting Cough Constipation Anemia	G 15(2.2) 15(2.2) 18(2.5) 3(0.4) 45(6.2) 4(0.5) 6(0.8) 6(0.8) 11(1.5)	D 406(58.2) 4(0.6) 22(3.1) 9(1.3) 55(7.7) 8(1.1) 5(0.7) 13(1.8) 15(2.1)
Maruyama 2008 V-15-32 (28) phase 3	245/244 244/239	Gefitinib 250 mg/day Docetaxel 60 mg/m^2	FACT-L - 23.4% vs 13.9%; p=0.023 TOI - 20.5% vs 8.7%; p=0.002 LCS - 22.7% vs 20.4% p=0.562	Grades 3-4 (%) Rash/acne Diarrhea Constipation Nausea Pruritus Vomiting Fatigue Paronychia Neutropenia	G 1(0.4) 5(2) 14(5.7) 5(2) 0 4(1.6) 1(0.4) 1(0.4) 20(8.2)	D 1(0.4) 2(0.8) 6(2.5) 9(3.8) 0 3(1.3) 6(2.5) 0 176(73.6)
Lee 2010 ISTANA (26) phase 3	82 79	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	FACT-L - Gefitinib 27.9% vs 27.3% p=0.9310 TOI - Gefitinib 26.5% vs 13/6% p=0.0641 LSC - Gefitinib 39.7% vs 37.9% p=0.8282	Grade 3 & 4 (%) Diarrhea Nausea Constipation Vomiting Cough Dyspnea Rash/acne Pruritus	G 1(1.2) 0 0 0 0 3(3.7) 3(3.7) 2(2.5)	D 0 0 0 0 0 3(3.9) 0 1(1.3)
Vamvakas 2010 (abstr) (49) phase 3	147 150	Pemetrexed 500 mg/m^2 Erlotinib 150 mg/day	NR	There was more grade 3-4 hematologic (neutropenia and thrombocytopenia) toxicity in the Pemetrexed arm and skin rash in the Erlotinib arm		
Ciuleanu 2012 TITAN(17) phase 3	203 221	Erlotinib 150 mg/day docetaxel or pemetrexed dose determined by centre	From FACT-L – median time to symptom progression 7.1 weeks for E and 9.0 weeks for chemotherapy (HR 1.19; 95 %CI 0.90-1.57; p=0.22	Grade 3 & 4 (%) Rash Pruritus Diarrhea Nausea Vomiting Fatigue Neutropenia Paronychia	Erlotinib 9(5) 0 5(3) 1(<1) 0 0 1(<1) 0	Chemo 0 0 0 1(<1) 0 1(<1) 8(4) 0
Karampeazis A 2013 (41) Phase 3	179 178	Erlotinib 150 mg/day Pemetrexed 500mg m^2	NR	Grade 3&4 (%) Neutropenia Anemia Thrombocytopenia Nausea Vomiting Diarrhea Fatigue Rash	P 11 (6.6) 2(1.2) 6(3.6) 0 0 1(0.6) 12(7.2) 0	E 0 1(0.6) 0 2(1.2) 1(0.6) 1(0.6) 1(0.6) 9(5.4)
Cufer 2006 SIGN (57) phase 2	68 73	Gefitinib 250 mg/day Docetaxol 75 mg/m^2	Symptom improvement rates 36.8% Median time to improvement 22 days	Grades 3-4 (%) Diarrhea Rash Pruritus	G 2(2.9) 2(2.9) 2(2.9)	D 3(4.2) 2(2.8) 0

			Symptom improvement rates 26% Median time to improvement 27 days	Dyspnea Vomiting Nausea Neutrophil count Febrile neutropenia	6(8.8) 1(1.5) 1(1.5) 1(1.5) 0	4(5.6) 1(1.4) 1(1.4) 29(46) 2(3.2)
Hong 2010 (abstr) (96) phase 2	32 34	Pemetrexed 500 mg/m^2 Gefitinib 250 mg/day	NR	Skin rash (44.1%) and anorexia (38.2%) for Gefitinib Fatigue (46.9%) and anorexia (40.6%) for pemetrexed Diarrhea was more frequent in patients with Gefitinib No grade 4 AE reported		
Kelly 2012(65) phase 2	101 100	Erlotinib 150 mg/day Pralatrexate 190 mg/m^2	NR	Grades 3 & 4 (%) Fatigue Dyspnea Rash Diarrhea Neutropenia	Erlotinib 5(5) 8(8) 8(8) 3(3) 2(2)	Pralatrexate 9(9) 6(6) 1(1) 1(1) 6(6)

Second-line EGFR Inhibitor vs EGFR Inhibitor Plus Chemotherapy in Unselected Patients

Five studies evaluated an EGFR inhibitor vs an EGFR inhibitor plus chemotherapy. Three of these trials all involved small patient numbers (54,55,92). There are four fully published papers (54,55,82,92) and one abstract (93). The results of these trials can be seen in Table 13.

There is no clear improvement in the response rate of an EGFR TKI in combination with another agent in comparison to an EGFR TKI alone. Small improvements in PFS were noted in many trials in favour of the combination arm, but none of the studies reached significance (54,55,82,92,93). Overall survival followed a similar pattern. All but one of the studies (92) showed that overall survival was longer with the EGFR inhibitor plus another agent. One study did reach significance (93). The majority of these trials are small trials, not powered adequately to detect differences in overall survival, so it is not possible to draw any real conclusions from these data.

Table 13. Second-line EGFR inhibitor vs an EGFR inhibitor plus chemotherapy in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Chen 2007(55) phase 2	Failed ≥2 regiments including taxanes and platinum-based chemotherapy Diagnosis of stage IV adenocarcinoma	27 21	Gefitinib 250 mg/day Vinorelbine 15 mg/m^2+ Gefitinib 250 mg/day	55.6% (15/27) 52.4% (11/21) p=0.837	Median TTP 7.1 months 12.8 months p=0.1331	13.3 months 1 year 51/3% 23.4 months p=0.1231 1 year 75.3 p=0.133
Aparisi 2011 (abstr) (92) phase 2	Advanced NSCLC Progressed on previous platinum therapy	34 36	Docetaxol 75 mg/m^2 + intermittent Erlotinib 150 mg/day Erlotinib 150 mg/day	NR	2.3 months 95% CI 1.9-3.1 3.1 months 95% CI 2.0-4.5	4.9 months 95% CI 2.7- 6.0 months 95% CI 2.5-6.0
Chen 2011 (54) phase 2	Failed previous chemotherapy Stage IIIB with malignant pleural effusion or stage IV adenocarcinoma PS 0-3	58 57	Gefitinib 250 mg/day UFT-Tegafur/uracil 1 capsule orally/day + Gefitinib 250	35% 37% p=0.847	5.3 months 1 year 18% 8.3 months 1 year 36.7% HR 0.65 (95% CI 0.43-0.97)	18.3 months 1 year 64.8% 2 year 27.7% 23.6 months 1 year 68.1% 2 year 47.1 %

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
			mg/day			
Aparisi 2012 (abstr) (93) phase 2	Advanced NSCLC	34 36	Docetaxol 75 mg/m^2 + intermittent Erlotinib 150 mg/day followed by Erlotinib 150 mg/day monotherapy Erlotinib 150 mg/day	NR	2.7 months 2 months p=0.08	11 months 95% CI 4.5-13.4 4.7 months 95% CI 2.5-6.6, p=0.02
Aerts JG 2013 NVALT-10 (82) Phase 2	Locally advanced or metastatic NSCLC Had 1st line platinum chemotherapy PS 0-2	115 116	Erlotinib 150mg/day Erlotinib 150mg/day on day 2-16 every 21 days + docetaxel 75 mg/m^2 for squamous or pemetrexed 500 mg/m^2 for non-squamous	NR	4.9 months 6.1 months HR 0.76; 95% CI 0.58-1.02, p=0.06	5.5 months 7.8 months HR 0.67; 95% CI 0.49-0.91, p=0.01

Symptom control and quality of life were evaluated in two studies (54,55). Both studies found no difference in symptoms between the two groups using the Lung Cancer Symptom Scale. These results can be seen in Table 14. Adverse effects were consistent with those known for EGFR inhibitors and chemotherapy.

Table 14. Quality of life and adverse effects of second-line EGFR inhibitor vs an EGFR inhibitor plus chemotherapy in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Symptom control/Quality of life	Adverse effects		
Chen 2007(55) phase 2	27 21	Gefitinib 250 mg/day Vinorelbine 15 mg/m^2 + Gefitinib 250 mg/day	No difference in symptoms between the two groups 25/20 patients completed the lung cancer symptoms scale	Grade 1-2 (3-4) Neutropenia Anemia Thrombocytopenia Fatigue Rash Dry skin Paronychia Diarrhea Constipation	Gefitinib 2(0) 13(0) 3(0) 2(0) 14(1) 5(1) 5(0) 5(0) 1(1)	V + G 0(1) 15(0) 1(0) 6(0) 5(2) 4(0) 4(0) 3(0) 1(0)
Aparisi 2011 (abstr) (92) phase 2	34 36	Docetaxol 75 mg/m^2 + intermittent Erlotinib 150 mg/day Erlotinib 150 mg/day	NR	Side effects were all tolerable		
Chen 2011(54) phase 2	58 57	Gefitinib 250 mg/day UFT-Tegafur/uracil 1 capsule orally/day + Gefitinib 250 mg/day	No difference in symptoms between the two groups 54/49 patients completed the lung cancer symptoms scale	Grade 1-2 (3-4) Skin rash Paronychia	G 1 0	G+UFT (0) (1)

Aparisi 2012(abstr) (93) phase 2	34 36	Docetaxol 75 mg/m^2 + intermittent Erlotinib 150 mg/day followed by Erlotinib 150 mg/day monotherapy Erlotinib 150 mg/day	NR	Skin rash and diarrhea were all tolerable
Aerts JG 2013 NVALT-10 (82) Phase 2	115 116	Erlotinib 150mg/day Erlotinib 150mg/day on day 2-16 every 21 days + docetaxel 75 mg/m^2 for squamous or pemetrexed 500 mg/m^2 for non-squamous	NR	Febrile neutropenia in 6% in combination arm.

Second-line EGFR Inhibitor Alone or in Combination With a Targeted Agent in Unselected Patients

Seventeen studies examined an EGFR inhibitor alone or in combination with a targeted agent (Table 15). Many of these trials are small, randomized phase II trials. Twelve studies evaluated an EGFR inhibitor versus an EGFR inhibitor plus another targeted agent (24,33,61,71,78,79,81,84,86,89,100,101), and five additional studies examined various combinations of EGFR inhibitors and targeted agents (31,62,74,76,94). There was no clear trend in response rate. Some results favoured the EGFR inhibitor alone (71,79), some favoured the combination arm (33,62,78,81,84,86,89), and some found no difference between groups (31,76). Significance was reached in the Scagliotti et al trial comparing erlotinib and high-dose celecoxib against erlotinib and placebo (10.6% vs 6.9%, p=0.0471) (33). PFS followed the same trend as response rate. Many trials found the combination of an EGFR inhibitor and a targeted agent resulted in longer survival. However, statistical significance was reached in only one of these trials (p=0.491) (61). Two trials had a longer PFS with the EGFR inhibitor (71,94). No difference was seen in six trials (31,62,81,84,86,89). The trial by Natale et al saw a significant increase in PFS with vandetanib (11 weeks) compared with gefitinib (8 weeks) (HR 0.69; 95% CI 0.50-0.96, p=0.025) (74). However, this observation was not confirmed in a subsequent phase III trial. Overall survival did not show any difference between groups in thirteen of the trials (24,31,33,61,62,71,74,78,79,81,84, 86,89). The only trial that showed an increase in overall survival was the study by Ramalingam at al. Overall survival was 12.1 months with erlotinib and R1507 16/mg/kg/wk (90% CI, 7.8-15.2) vs 8.1 months for erlotinib (90% CI, 4.8-10.3) and placebo, and 8.1 months for erlotinib plus R1507 9/mg/kg/every three weeks (90%CI, 6-10) (76). Several of these compounds have moved into phase III clinical trials, but there is currently no evidence to support the combination of another targeted agent with erlotinib.

Table 15. Second-line EGFR inhibitor alone or in combination with a targeted agent in unselected patients.

Reference	Inclusion Criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Herbst 2011 BeTa(24) phase 3	Advanced-stage NSCLC that was recurrent or refractory after chemotherapy or chemoradiation PS 2 or lower	317/313 319/313	Erlotinib 150 mg/day + Placebo Bevacizumab 15 mg/kg + Erlotinib 150 mg/day	19 (6%) 38 (13%)	1.7 months IQR 1.3-4.1 3.4 months IQR 1.4-8.4 HR 0.62 (0.52-0.75)	9.2 months 1 year 40.7% 9.3 months 1 year 42.1 HR 0.97 (0.80-1.18) p=0.7583
Scagliotti 2012 (33) phase 3	IIIB/IV NSCLC Patients who have progressed on one line of therapy or refused standard chemotherapy	480 480	Erlotinib 150 mg/day + Sunitinib 37.5 mg/day Erlotinib 150 mg/day + placebo	10.6% 6.9% p=0.0471	3.6 months 2.0 months HR 0.807; 95% CI 0.695-0.937	9.0 months 8.5 months HR 0.922; 95% CI 0.797-1.067, p=0.1388
Natale 2011 (31) phase 3	Locally advanced or metastatic stage IIIB or IV NSCLC Failure of 1 or 2 prior chemotherapy regimens PS 0-2	617 /614 623/623	Erlotinib 150 mg/day Vandetanib 300 mg/day	12% 12% p=0,98	2.0 months 2.6 months HR 0.98; 95% CI 0.87-1.10, p=0.721	7.8 months 6.9 months HR 1.01; 95.08% CI, 0.89-1.16, 2 sides p=0.830
Lynch 2009 (71) phase 2	Relapsed or refractory locally advanced or metastatic NSCLC stage IIIB or IV PS ≤1. Received chemotherapy for stage IIIB or IV (excluding adjuvant or neoadjuvant)	25/25 25/22	Erlotinib 150 mg/day Erlotinib 150 mg/day + Bortezomib 1.6 mg/m^2	4(16%) 2(9%)	TTP 2.7 months PFS 2.7 months TTP 1.5 months PFS 1.3 months	7.3 months. 1 year 40% 8.5 months 1 year 30%
Besse B 2013 (84) phase 2	Advanced progressive NSCLC PS 1	66 67	Everolimus 5mg/day + Erlotinib 150 mg/day Erlotinib 150 mg/day	12.1% (95%CI 5.4-22.5) 10.4% (95% CI 4.3-20.3)	2.9 months 95%CI 2.4-3.9 2.0 months 95% CI 1.1-2.8	9.1 months 9.7 months
Groen 2013 (86) phase 2	Stage IIIB/IV NSCLC PS 0-1 2 prior treatments	65	Sunitinib 37.5 mg/day + Erlotinib 150	4.6%	2.8 months	8.2 months 95% CI 5.70- 11.30

	including 1 platinum regimen	67	mg/day Placebo + Erlotinib 150 mg/day	3.0%	2.0 months HR 0.898; 80% CI 0.671-1.203; p=0.321	7.6 months 95% CI 5.30-13.40 HR 1.066; 95% CI 0.705-1.612, p=0.617
Schiller 2010 Arq 197-209 (abstr) (101) phase 2	NSCLC EGFR inhibitor naïve patients	84 83	Erlotinib 150 mg/day + ARQ 197 – dose not given Erlotinib 150 mg/day + placebo	NR	16.1 weeks 9.7 weeks HR 0.81; 95% CI 0.57-1.15, p=0.23	NR
Han 2011 (61) phase 2	IIIB/IV NSCLC Failure of 1 platinum based chemotherapy PS <3 Life expectancy >12 weeks	54 52	Gefitinib 250 mg/day Gefitinib 250 mg/day + Simvastin 40 mg/day	31.5% 38.5%	1.9 months 3.3 months HR 0.891; 95% CI 0.604-1.315, p=0.491	12 months 13.6 months HR 0.876; 95% CI 0.567-1.354, p=0.491
Sequist 2011 (78) phase 2	Advanced NSCLC Previously treated with ≥ chemotherapy regimen PS 0-1	84 83	Erlotinib 150 mg/day + Tivatinib 360 mg Erlotinib 150 mg/day + placebo	10% 7%	3.8 months 2.3 months HR 0.81; 95% CI 0.57-1.16; p=0.24	8.5 months 6.9 months HR 0.87; 95% CI 0.59-1.27; p=0.47
Spigel 2011 (79) phase 2	NSCLC, PS;0-2 1 or 2 prior chemotherapy regimens	112/111 56/55	Erlotinib 150 mg/day + Sorafenib 400 mg twice a day Erlotinib 150 mg/day + placebo	8% (95%CI 4-15) 11% (95%CI 4-22)	3.38 months 6 months 29% 1.94 months 6 months 22% HR 0.86; 95% CI 0.60-1.22, 1-sided p=0.196	7.62 months 7.23 months HR 0.89; 95% CI 0.59-1.34, 1-sided p=0.290
Reckamp 2012 (abstr) (100) phase 2	IIIB/IV NSCLC Patients who have progressed on one line of therapy or refused standard chemotherapy	54 53	Erlotinib 150 mg/day + high dose celecoxib 600mg/ twice a day Erlotinib 150 mg/day + placebo	NR	5.4 months 2.9 months p=0.31	NR
Witta 2012 (81) phase 2	IIIB/IV NSCLC Treatment with one	65	Erlotinib 150 mg/day + placebo	9.2%	1.88 months	6.7 months

	chemo regimen including platinum PS 0-1	67	Erlotinib 150 mg/day + Entinostat 10 mg	3.0	1.97 months HR 0.99; 95% CI 0.68-1.44, p=0.98	8.9 months HR 0.85; 95% CI 0.59-1.23, p=0.39
Natale 2009 (74) phase 2	Stage IIIB/IV NSCLC after failure of first-line with or without second-line chemotherapy. PS 0 or 1	85 83	Gefitinib 250 mg/day Vandetanib 300 mg/day	PR 1% PR 8%	8.1 weeks 11 weeks HR 0.69; 95% CI 0.50-0.9, p=0.025	No advantage in OS was seen HR 1.19; 95% CI 0.84-1.68, p=0.34
Ramalingam 2011 (76) phase 2	NSCLC stage IIIB or IV PS 0-2. Progression after 1-2 chemotherapy regimens	57/57 58/57 57/57	Erlotinib 150 mg/day + placebo Erlotinib 150 mg/day + R1507 9 mg/kg/wk Erlotinib 150 mg/day + R1507 16 mg/kg	8.8% 90% CI 3.5-17.6 8.8% 90% CI 2.4-15.3 7% 90% CI 2.4-15.3	1.5 months 90% CI 1.45-2.91 1.87 months 90% CI 1.41-2.91 2.7 months 90% CI 2.1-3.9	8.1 months 90% CI 4.8-10.3 8.1 months 90% CI 6-10 12.1 months 90% CI 7.8-15.2
Herbst 2007 (62) phase 2	Locally advanced or metastatic NSCLC Progression after one platinum-based chemotherapy regimen	39 40 41	Bevacizumab 15 mg/kg + Erlotinib 150 mg/day Bevacizumab 15 mg/kg + Docetaxol 75 mg/m^2 or Pemetrexed 500 mg/m^2 Docetaxol 75 mg/m^2 or Pemetrexed 500 mg/m^2 + placebo	17.9% 12.5% 12.2%	4.4 months 4.8 months 3.0 months	13.7 months 1-year survival 57.4% 12.6 months I-year survival 53.8% 8.6 months 1-year survival 33.1%
Gian 2012 (abstr) (94) phase 2	IIIB/IV NSCLC PS 0-2 ≤2 lines of therapy with the last being Erlotinib. Patients must have progressive disease following clinical benefit	24 28	Erlotinib 150 mg/day + Sorafenib 400 mg x2 day Sorafenib 400 mg	NR	3.1 months 95% CI 1.7-3.7 2.3 months 95% CI 1.7-3.6 p=0.84	NR
Spigel DR 2013	IIIB/IV NSCLC	69	Onartuzumab 15	5.8%	2.2 months	8.9 months

(89) Phase 2	1 or 2 previous chemotherapy regimens (including platinum based) PS ≤ 2	68	mg/kg + erlotinib 150 mg/day Erlotinib 150 mg/day + placebo	4.4%	2.6 months HR 1.09, p=0.69	7.4 HR 0.80, p=0.34

The data on quality of life and adverse effects can be seen in Table 16. Symptom control and quality of life were reported in two studies. The study by Scagliotti et al also found no statistical difference in mean EQ-5D Health Index score between treatment groups (p=0.3373) (33). The study by Natale et al found the EORTC QLQ-C30 was similar between groups: erlotinib 80% and vandetanib 82% (31). Adverse effects were in line with those commonly associated with EGFR inhibitors and chemotherapy.

Table 16. Adverse effects in second-line EGFR inhibitor alone or in combination with another agent in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Adverse effects		
Herbst 2011 BeTa(24) phase 3	317/313 319/313	Erlotinib 150 mg/day + Placebo Bevacizumab 15 mg/kg + Erlotinib 150 mg/day	Grade 3-4 (%) Haemorrhage Arterial thromboembolic event Hypertension rash	E 7(2) 1(1) 4(1) 19(6)	B+E 8(3) 10(3) 15(5) 49(16)
Natale 2011 (31) phase 3	617 /614 623/623	Erlotinib 150 mg/day Vandetanib 300 mg/day	Grade 3 or 4 (%) Diarrhea Rash Nausea Fatigue Dyspnea Cough Vomiting Pruritus	E 21(3) 23(4) 10(2) 22(4) 38(6) 5(0.8) 12(2) 0	V 29(5) 18(3) 7(1) 27(4) 27(4) 5(0.8) 10(2) 3(0.5)
Scagliotti 2012 (33) phase 3	480 480	Erlotinib 150 mg/day + sunitinib 37.5 mg/day Erlotinib 150 mg/day + placebo	Grades 3 & 4 (%) Diarrhea Fatigue Nausea Vomiting Neutropenia	S+E (15.8) (8) (1.7) (1.7) (4.6)	E+placebo (2.9) (3.3) (0.6) (0.6) (0.7)
Lynch 2009 (71) phase 2	25/25 25/22	Erlotinib 150 mg/day Erlotinib 150 mg/day + Bortezomib 1.6 mg/m^2	Grade 3 (%) Rash Diarrhea Nausea/vomiting Paresthesia Peripheral Neuropathy	E 3(12) 0 0 1(4) 0	B+E 3(10) 1(3) 1(3) 0 1(3)
Besse B 2013 (84) phase 2	66 67	Everolimus 5mg/day + Erlotinib 150 mg/day Erlotinib 150 mg/day	Most common grade 3-4 AEs: Dyspnea (6%) and Diarrhea (5%) in Erlotinib Stomatitis (32%), asthenia (11%) and diarrheal (8%) in everolimus + Erlotinib.		
Groen 2013 (86) phase 2	65 67	Sunitinib 37.5 mg/day + Erlotinib 150 mg/day Placebo + Erlotinib 150 mg/day	Grade 3&4 (%) Diarrhea Rash Fatigue Nausea Thrombocytopenia	E+ S 11(17) 5(8) 6(9) 3(5) 4(6)	P 1(2) 2(3) 2(3) 0 0
Schiller 2010 Arq 197-209 (abstr) (101) phase 2	84 83	Erlotinib 150 mg/day + ARQ 197 – dose not given Erlotinib 150 mg/day + placebo	 Rash Diarrhea Fatigue Nausea Anemia	E+A 64 48 33 26 14	E+P 52 53 37 26 13
Han 2011 (61) phase 2	54 52	Gefitinib 250 mg/day Gefitinib 250 mg/day + Simvastin 40 mg/day	Grade 3 & 4 (%) Rash Dry Skin Diarrhea Nausea	G 1(2) 0 0 0	G+S 2(4) 0 0 0
Ramalingam 2011(76) phase 2	57/57 58/57	Erlotinib 150 mg/day + placebo Erlotinib 150 mg/day + R1507 9	Grades 3-4 (%) Anemia Cough	E 5 0	E+Rw 2 0	E+Rx3w 0 0

	57/57	mg/kg/wk Erlotinib 150 mg/day + R150716 mg/kg	Diarrhea 2 5 2 Dyspnea 7 2 4 Fatigue 7 13 7 Nausea 0 5 0 Paronychia 0 0 0 Rash 7 8 11
Sequist 2011 (78) phase 2	84 83	Erlotinib 150 mg/day + Tivatinib 360 mg Erlotinib 150 mg/day + placebo	Grades 3-5 (%) E+T E Diarrhea 6(7.1) 6(7.2) Dyspnea 6(7.1) 11(13.3) Fatigue 4(4.8) 5(6) Nausea 1(1.2) 4(4.8) Neutropenia 4(4.8) 2(2.4) Pruritus 0 2(2.4) Rash 8(9.5) 6(7.2) Thrombocytopenia 0 0 Vomiting 3(3.6) 1(1.2)
Spigel 2011 (79) phase 2	112/111 56/55	Erlotinib 150 mg/day + Sorafenib 400 mg X2 day Erlotinib 150 mg/day + placebo	Grades 3 & 4 (%) E+S E Anemia 7(6) 3(5) Neutropenia 4(4) 0 Thrombocytopenia 1(1) 0 Diarrhea 17(15) 0 Rash 7(6) 7(13) Fatigue 15(4) 5(9)
Witta 2012 (81) phase 2	480 480	Erlotinib 150 mg/day + Sunitinib 37.5 mg/day Erlotinib 150 mg/day + placebo	Grades 3 & 4 (%) Erlotinib + placebo Erlotinib + Entinostat Fatigue 10(16) 13(20) Rash 3(5) 7(11) Dyspnea 2(3) 6(9) Diarrhea 4(6) 2(3)
Natale 2009 (74) phase 2	85 83	Gefitinib 250 mg/day Vandetanib 300 mg/day	Grade 3 or 4 (%) **G** **V** Diarrhea 36(42) 54(65) Fatigue 35(40) 40(48) Nausea 26(30) 24(29) Rash 19(22) 28(24) Dyspnea 21(24) 29(35) Vomiting 18(21) 5(6) Rash 11(13) 6(7)
Herbst 2007 (62) phase 2	39 40 41	Bevacizumab 15 mg/kg+ Erlotinib 150 mg/day Bevacizumab 15 mg/kg + Docetaxol 75 mg/m^2 or pemetrexed 500 mg/m^2 Docetaxol 75 mg/m^2 or Pemetrexed 500 mg/m^2 + placebo	Grades 3 & 4 B+E B + chemo chemo Fatigue 3 5 5 Nausea 2 2 1 Vomiting 0 2 1 Dyspnea 2 4 4 Rash 1 0 0 Neutropenia 2 8 7 Anemia 0 2 0 Cough 0 0 1 Diarrhea 3 0 0
Gian 2012 (abstr) (94) phase 2	24 28	Erlotinib 150 mg/day + Sorafenib 400 mg x2 day Sorafenib 400 mg	No grade 3 or 4 hematologic toxicities in either arm except for grade 3 anemia in 1 patient in the Erlotinib group
Spigel DR 2013(89) phase 2	69 68	Onartuzumab 15 mg/kg + erlotinib 150 mg/day Erlotinib 150 mg/day + placebo	Grade 3&4 (%) E + O E Rash 7(10.1) 2(3) Diarrhea 5(7.2) 3(4.5) Fatigue 6(8.7) 2(3) Nausea 0 2(3) Vomiting 4(5.8) 13(19.4)

Second-line EGFR Inhibitor Plus Chemotherapy Versus Chemotherapy in Unselected Patients

One study examined the use of an EGFR inhibitor plus chemotherapy versus chemotherapy alone. This study was only available as an abstract (103). The results of this study can be seen in Table 17. This study demonstrated a greater response rate and longer PFS for chemotherapy plus an EGFR inhibitor. The result for PFS is significant (HR 0.63; 95% CI 0.44-0.90, p=0.005). In addition, overall survival was prolonged in the combined arm, and this result was significant (HR 0.68; 95% CI, 0.47-0.98, p=0.019) (103). Quality of life and adverse effects were not reported in this abstract. Given the small size of this trial, the combination of an EGFR TKI plus chemotherapy is not recommended.

Second-line EGFR Inhibitor Vs Placebo in Unselected Patients

Three fully published studies examined the use of an EGFR inhibitor against a placebo (8,18,37). The results can be seen in Table 18. In the trial by Shepherd et al, the response rate was significant with erlotinib (p<0.001) (8). In the trial by Thatcher et al, the response rate was higher with gefitinib, and significance was reached (p<0.0001) (37). The median PFS was longer in the EGFR group for all three trials. It was significant in the Shepherd et al (p<0.001) (8) and Gaafar et al trials (p=0.002) (18). There was no difference between groups for overall survival in the Thatcher et al and Gaafar et al trials (18,37). The overall survival rate was significant in the trial by Shepherd et al (p<0.001) (8).

The study by Tsao et al evaluated tumour samples in the BR21 study by Shepherd et al and reported on the outcomes of EGFR mutational status, EGFR protein expression and EGFR gene copy number. Survival was longer in the erlotinib group compared to the placebo group when EGFR protein was overexpressed (HR 0.68; 95% CI 0.49-0.95, p=0.02) (113).

Symptom control and quality of life were addressed in two studies (8, 37). These data can be seen in Table 19. Time to deterioration of cough (p=0.04), dyspnea (p=0.03) and pain (p=0.04) symptoms was prolonged and significant with erlotinib in the study by Shepherd et al (8). Symptom improvement was significant with gefitinib in the study by Thatcher et al (p=0.019) (37). Adverse effects were also in line with those associated with EGFR inhibitor use.

Second-line EGFR Inhibitor Vs EGFR Inhibitor in Unselected Patients

Five studies examined the use of an EGFR inhibitor against an EGFR inhibitor. Four studies were fully published (43,58,67,75), and one was in abstract form (91). The results can be seen in Table 20. IDEAL 1 and 2 trials compared two dose levels of gefitinib and found no difference in any of the reported outcomes. Similarly, the ICOGEN trial comparing gefitinib and icotinib reported no difference in outcomes. A randomized phase II trial comparing dacomitinib and erlotinib demonstrated a significant improvement in response rate and PFS in favour of dacomitinib, along with a trend towards improvement in overall survival (75). These findings require confirmation in a phase III trial, however. Median overall survival showed no difference between groups in the other trials (43,58,67).

Quality of Life was addressed in the two IDEAL studies. There were no differences between the different doses of gefitinib for symptom response (58,67). Adverse effects were consistent with those known for EGFR inhibitors. The adverse effects were slightly elevated with the 500mg/day dose of gefitinib

Table 21 shows the adverse events of second-line EGFR inhibitor vs EGFR inhibitor in unselected patients.

Table 17. Second-line EGFR inhibitor plus chemotherapy vs chemotherapy in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Von Pawel 2011 (abstr)(103) phase 2	Non-squamous NSCLC After failure of platinum therapy for advanced or metastatic disease PS ≤2 ≥1 measureable lesion by RECIST	86 79	Pemetrexed 500 mg/m^2 Pemetrexed 500 mg/m^2 + Erlotinib 150 mg/day	10.8% 17.1%	2.9 months 95% CI 1.9-3.4 3.2 months 95% CI 2.9-4.7 HR 0.63; 95% CI 0.44-0.9, p=0.005	7.8 months 95%CI 5.3- 10.4 11.8 months 95%CI 8.2-16.7 HR 0.68; 95% CI 0.47-0.098, p=0.019.

Table 18. Second-line EGFR inhibitor vs placebo in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Progression-free survival	Median overall survival
Shepherd 2005 BR21 (8) phase 3	1-2 prior CT regimens with at least 1 combination CT if age <70 years, stage IIIB or IV NSCLC, PS 0-3	488 / 488 243 / 243	Erlotinib 150 mg/day placebo	8.9% <1% p<0.001	2.2 months 1.8 months HR 0.61; 95% CI 0.51-0.7, p<0.001	6.7 months / 31% 4.7 months / 22% HR 0.70; 95% CI 0.58-0.85, p<0.001
Thatcher 2005 ISEL (37) phase 3	1-2 prior CT regimens, refractory or intolerant to latest CT regimen, locally advanced or metastatic NSCLC	1129 563	Gefitinib 250 mg/day placebo	8.0% 1.3% p<0.0001	Median time to treatment failure 7.2 months 2.6 months	5.6 months 5.1 months HR 0.89; 95% CI 0.77-1.02; p=0.087 log rank)
Gaafar 2011 EORTC 08021/ILCP 01/03(18) phase 3	Stage IIIB or IV NSCLC non progressing after prior platinum based chemotherapy (2-6 cycles) PS ≤ 2	86 87	Gefitinib 250 mg/day Placebo	NR	4.1months 2.9 months HR 0.61; 95% CI 0.45-0.83, p=0.002	Median after 41 months 10.9 95% CI 9.2-13.8 9.4 months 95% CI 6.6-13.8 HR 0.81; 95% CI 0.59-1.12, p=0.204

Table 19. Adverse effects and quality of life for second-line EGFR inhibitor vs placebo in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Quality of life	Adverse effects

Shepherd 2005
BR21 (8)
phase 3
	488 / 488
	
	243 / 243
		Erlotinib 150 mg/day
		
		Placebo
			Time to symptom deterioration longer with erlotinib:
			cough, 4.9 vs 3.7 months, p=0.04;
			dyspnea, 4.7 vs 2.9 months, p=0.03;
			pain, 2.8 vs 1.9 months, p=0.04.
				Grade 3-5 Erlotinib Placebo
				Nausea 3% 5%
				Vomiting 3% 2%
				Diarrhea 6% <1%
				Fatigue 19% 23%
				Rash 9% 0%

Thatcher 2005 ISEL (37) phase 3	1129 563	Gefitinib 250 mg/day Placebo	QOL improvement on LCS, 25.5% and 17.9%, p=0.068) Symptom improvement greater with gefitinib, p=0.019	Grades 3 & 4(%) Gefitinib Placebo Rash 18(2) 1 Diarrhea 31(3) 5(1) Nausea 9(1) 2 Vomiting 13(1) 2 Pruritus 4 1 Cough 2 4 Dyspnea 35(3) 21(4) Paronychia 1 0
Gaafar 2011 EORTC 08021/ILCP 01/03 (18) phase 3	86 87	Gefitinib 250 mg/day Placebo	NR	Grades 3 & 4 G P Fatigue 4 1 Rash 2 0 Diarrhea 1 0 Pain 4 6 Dyspnea 4 6

Table 20. Second-line EGFR inhibitor vs EGFR inhibitor in unselected patients.

Reference	Inclusion criteria	Number enrolled/ analyzed	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival
Shi 2013 ICOGEN (43) phase 3	Previous chemotherapy NSCLC	200 199	Icotinib 125mg tid Gefitinib 250 mg/day	ORR 27.6% 27.2%	4.6 months 95% CI 3.5-6.3) 3.4 months 95%CI 2.3-3.8 HR 0.84; 95% CI 0.67-1.0, p=0.13	13.3 months 13.9 months HR 1.02; 95% CI 0.82-1.27, p=0.57
Kris 2003 IDEAL2 (67) phase 2	2 or more prior CT regimens containing platinum and	106 / 102	Gefitinib 250 mg/day + placebo	12% (12/102) 95% CI 6-20	NR	Median: 7 months Projected 1-year: 27% Median: 6 months, p=0.40

	docetaxel, stage IIIB or IV NSCLC, PS 0-2, symptomatic (LCS FACT-L score ≤ 24)	115 / 114	Gefitinib 500 mg/day (2 x 250 mg)	9% (10/114) 95% CI, 4-16 p=0.51		Projected 1-year: 24%, p=0.54
Fukuoda 2003 IDEAL1 (58) phase 2	1-2 prior CT regimens, at least 1 platinum-based, stage III/IV NSCLC not curable by surgery or RT, PS 0-2	104 / 103 106 / 106	Gefitinib 250 mg/day Gefitinib 500 mg/day	17.5% 19%	2.7 months 2.8 months	7.6 months, 95% CI 5.3-10.1 1-year: 35% 8.0 months, 95% CI 6.7-9.9 1-year: 29%
Ahn 2010 (abstr)(91) phase 2	NSCLC stage IIIB/IV Failure of previous chemotherapy	48 48	Erlotinib 150 mg/day Gefitinib 250 mg/day	39.6% 47.9% p=0.411	3.1 months 4.9 months HR 0.81; 95% CI 0.52-1.25; p=0.336	NR
Ramalingam 2012 (75) phase 2	Advanced NSCLC PS 0-2 Progression after 1 or 2 prior chemotherapy treatments	94 94	Dacomitinib 45mg/day Erlotinib 150 mg/day	17.0% 5.3% p=0.011	2.86 months 1.91 months HR 0.66; 95% CI 0.47-0.91, p=0.012	9.53 months 7.44 months HR 0.80, 95% CI 0.56 – 1.1, p=0.205

ORR = overall response rate.

Table 21. Adverse events of second-line EGFR inhibitor vs EGFR inhibitor in unselected patients.

Reference	Number enrolled/ analyzed	Treatment	Adverse effects		
Shi 2013 ICOGEN (43) phase 3	200 199	Icotinib 125mg tid Gefitinib 250 mg/day	**Adverse response** Rash Diarrhea	**G** 49.2% 27.6%	**I** 39.5% 18.5%
Kris 2003 IDEAL2(67) phase 2	106 / 102 115 / 114	Gefitinib 250 mg/day + placebo Gefitinib 500 mg/day	Grade 3 & 4 Rash Diarrhea	500 mg 5(4) 6(5)	250 mg 0 1(1)
Fukuoda 2003 IDEAL1 (58) phase 2	104 / 103 106 / 106	Gefitinib 250 mg/day Gefitinib 500 mg/day	Grades 3&4 Rash Pruritus Diarrhea Nausea Anemia	500 mg 7 1 7 1 1	250 mg 1 0 0 1 8
Ahn 2010 (abstr) (91) phase 2	48 48	Erlotinib 150 mg/day Gefitinib 250 mg/day	More patients in the Erlotinib arm showed grade 3 skin rash		
Ramalingam 2012 (75) phase 2	94 94	Dacomitinib 45mg a day Erlotinib 150 mg/day	Grade 3 (%) Diarrhea Dermatitis Paronychia Rash Nausea Fatigue	D 11 (11.8) 10 (10.8) 3 (3.2) 2 (2.2) 2 (2.2) 1 (1.1)	E 4 (4.3) 6 (6.4) 1 (1.1) 1 (1.1) 1 (1.1) 1 (1.1)

Second-Line Clinically Selected Population

Four studies examined the use of EGFR inhibitors in a clinically selected population. Two were fully published trials (51,88), and two were in abstract form (45,106).

Second-line EGFR Inhibitor vs Chemotherapy in Clinically Selected Patients

Two trials compared pemetrexed with an EGFR as second-line therapy in never smokers (Table 22). The overall response rate was significantly higher for gefitinib (30.1% vs 14.9%, p<0.001) (45). PFS was significantly longer for patients randomized to gefitinib (9.4 months vs 2.9 months, p=0.010) and also for patients randomized to a combination of erlotinib and pemetrexed (7.4 months compared to 3.8 months for erlotinib and 4.4 months to pemetrexed HR 0.57; 95% CI 0.40-0.81, p=0.002) (88). However, the survival rates were comparable, and no significance was found (p=0.89) (45,88).

One study examined the use of gefitinib in non-squamous patients in the second line setting (Table 22)(106). There was no difference in response rate; however, PFS was significant for pemetrexed (4.8 months vs 1.6 months for gefitinib HR 0.51; 95% CI 0.36-0.73, p<0.001) (106). Overall survival was not yet reached for this trial.

Table 22. Second-line EGFR inhibitor vs chemotherapy in clinically selected patients.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate	Median progression-free survival	Survival	Adverse effects
Ahn 2011 KCSG-LU08-01 (abstr) (45) phase 3	Never smokers Previously treated with platinum-based chemo PS 0-2	Gefitinib 250 mg/day Pemetrexed 500mg/m^2	135 (not broken down)	ORR: 30.1% 14.9% (p < 0.001)	9.4 months 2.9 months (p = 0.010)	**1**-year survival 73.6% 70.5% (p = 0.89)	
Lee DH 2013 (88) Phase 2	Locally advanced or metastatic NSCLC Had failed 1 chemo regimen PS 0-2 Only never smoker	Erlotinib 150mg/day + Pemetrexed 500mg/m^2 Erlotinib 150mg/day Pemetrexed 500mg/m^2	78 82 80		7.4 months 3.8 months 4.4 months P+E vs single arms HR 0.57; 95% CI 0.40-0.81, p=0.002	20.5 months 22.8 months 17.7 months E+P vs single arms HR 1.08; 95% CI 0.69-1.67, p=0.747	Grade 3&4 (%) E+P E P Neutro-penia 18(24) 0 10(13) Anemia 8(11) 0 7(9) Rash 6(8) 5(6) 0 Diarrhea 7(9) 0 0
Yang J 2013 CTONG 0806 (106) abstr Phase 2	Locally advanced or metastatic NSCLC Non-squamous No mutations in exons 18-21 Previously treated with platinum-based chemo	Gefitinib 250mg.day Pemetrexed 500mg/m^2	81 76	14.7% 13.3% p=0.814	1.6 months 4.8 months HR 0.51; 95% CI 0.36-0.73, p<0.001	OS not yet mature	More skin rash and diarrhea in in Gefitinib arm and more fatigue and ALT in p arm

ORR = overall response rate; OS = overall Survival

Third/fourth-line EGFR Inhibitor vs Placebo in Clinically Selected Patients

The Lux Lung 1 trial evaluated afatinib in patients who had received one or two prior chemotherapy treatments, as well as gefitinib or erlotinib in a selected population of patients (Table 23). The response rate for afatinib vs placebo was 7% and 0.5%, respectively. There was a significant improvement in PFS for patients randomized to afatinib (3.3 months vs 1.1 months, p<0.0001). However, there was no difference in the primary outcome of overall survival (10.8 months vs 12 months, p=0.74). Adverse effects were consistent with those associated with EGFR inhibitors (51). Therefore, there is currently no evidence that further therapy with an EGFR TKI in patients who have already received gefitinib or erlotinib improves overall survival.

Table 23. Second-line EGFR inhibitor vs placebo in clinically selected patients.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate	Median progression -free survival	Median overall survival	Adverse effects		
Miller 2012 LUX-Lung1 (51) phase 2b/3	Stage IIIB/IV NSCLC Failed 1 or 2 lines of chemotherapy Had disease progression for 12 weeks after Erlotinib or Gefitinib PS 0-2	Afatinib 50 mg/day + BSC Placebo + BSC	390 195	7% 0.5%	3.3 months 1.1 months HR 0.38; 95% CI 0.31-0.48, p<0.0001	10.8 months 12.0 months HR 1.08; 95% CI 0.86-1.35, p=0.74	Grade 3 & 4 (%) Diarrhea Rash Fatigue Nausea Vomiting Pruritus Dyspnea Cough	Afatinib 66(17) 56 14) 23 (6) 8 (2) 9 (2) 1 (<1) 17 (5) 3(<1)	Placebo 0 0 3 (2) 0 1 (<1) 1 (<1) 9 (5) 5 (3)

Second-line Molecularly Selected Population

Four studies, three fully published (40,66,83) and one abstract (95), examined the use of EGFR inhibitors in molecularly selected patients.

Second-line EGFR Inhibitor vs Chemotherapy in Molecularly Selected Patients

One study examined the use of an EGFR inhibitor vs chemotherapy in patients known to be EGFR wild type (40). Improved PFS was observed for docetaxel compared with erlotinib (HR 0.71; 95% CI 0.53-0.95, p=0.02). The primary outcome in this trial was overall survival, which was also significant for docetaxel 8.2 months vs 5.4 months for erlotinib (HR 0.73; 95% CI 0.53-1.00, p=0.05) (40). (Table 24)

Second-line EGFR Inhibitor Plus Another Agent vs an EGFR Inhibitor In Molecularly Selected Patients

Two studies examined the use of an EGFR inhibitor plus another agent vs erlotinib in molecularly selected patients (83,95) (Table 25). Time to progression was significantly increased following erlotinib and apricoxib (p=0.018) in the Gitlitz trial (95), and no difference was seen in the Belani trial (83). However, overall survival favoured the erlotinib and placebo group (HR 0.4, p=0.025) in the Gitlitz trial (95). Once again no difference was seen between groups in the Belani trial (83). Adverse effects are in line with those associated with EGFR inhibitors.

Second-line EGFR Inhibitor vs EGFR Inhibitor in Molecularly Selected Patients

One study examined the use of an EGFR inhibitor vs an EGFR inhibitor in molecularly selected patients (66) (Table 26). The response rate and PFS were higher in the gefitinib group compared to the erlotinib group. Significance was not reached for PFS (p=0.336). Adverse effects are in line with those associated with EGFR inhibitors (66).

Table 24. Progression-free survival of second-line EGFR inhibitor vs chemotherapy in molecularly selected patients.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Median Progression free survival	Median Overall Survival	Adverse effects		
Garassino 2013 TAILOR (40) phase 3	EGFR wild type Previously treated with 1st-line platinum-based regimen	Erlotinib 150 mg/day Docetaxel 75 mg/m^2	112 110	2.4 months 2.9 months HR 0.71; 95% CI 0.53-0.95, p=0.02	5.4 months 8.2 months HR 0.73, 95% CI 0.53-1.00, p=0.05	Grades 3-4 (%) Neutropenia Diarrhea Nausea or vomiting Dermatological	E 0 3(3) 1(1) 15 (14)	D 21 (20) 2(2) 3(3) 0

Table 25. Second-line EGFR inhibitor plus another agent vs an EGFR inhibitor in molecularly selected patients.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Median progression-free survival	Median overall survival	Adverse effects		
Gitlitz 2011 Apricot-l (abstr) (95) phase 2	Stage IIIB/IV NSCLC	Erlotinib 150 mg day + Apricoxib 400 mg day Placebo + erlotinib 150 mg day	120 176	TTP 2.1 months TTP 1.8 months HR 0.5, p=0.018	5.6 months 5.9 months HR 0.4, p=0.025	Diarrhea 55% Rash 54% Fatigue 38% Nausea 33%		
Belani 2013 (83) Phase 2	Advanced NSCLC Previous chemotherapy EGFR positive	PF-3512676 (0.20 mg/kg)+ erlotinib 150mg/day Erlotinib 150mg/day	18 21	1.6 months 1.7 months HR 1.00; 95% CI 0.5-2.0, p=0.9335	6.4 months 4.7 months HR 1.3; 95% CI 0.6-2.8, p=0.4925	Grades 1-3 (%) Diarrhea Fatigue Rash Nausea	E+ PF-3512676 5(28) 4(22) 1(6) 1(6)	E 0 1(5) 2(10) 0

Table 26. Second-line EGFR inhibitor versus EGFR inhibitor in molecularly selected patients.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate	Median progression-free survival	Median overall survival	Adverse effects		
Kim 2012(66) phase 2	IIIB/IV NSCLC Failure of 1st-line chemo PS 0-2 EGFR mutation or 2 of 3 clinical factors associated with mutation (female, biology, never smoker)	Gefitinib 250 mg/day Erlotinib 150 mg/day	48 48	47.9% 39.6%	4.9 months 3.1 months p=0.336	Median OS has not been reached	Grades 1-3 (%) Skin Rash Paronychia Diarrhea Fatigue Nausea Vomiting	Gefitinib 30(62.5) 5(10.4) 16(33.4) 0 3(6.3) 1(2.1)	Erlotinib 35(72.9) 4(8.3) 17(35.5) 8(16.7) 2(4.2) 0

Maintenance

EGFR Inhibitors in Unselected Patients in the Maintenance Setting

There has been considerable interest in recent years in evaluating agents as maintenance therapy, in an attempt to improve the survival of patients with advanced NSCLC. Trials have evaluated continuing the same drug (continuation maintenance) or switching to another drug (switch maintenance). Five studies have examined EGFR inhibitors in unselected patients in the switch-maintenance setting. All are fully published papers (16,34,35,85,87).

One study examined the use of an EGFR inhibitor compared to chemotherapy in the maintenance setting (Table 27). Bylicki et al randomized patients to maintenance therapy with erlotinib, gemcitabine, or observation (85). In the observation group, patients received no treatment. There was no clear improvement in PFS for either erlotinib or gemcitabine. No significant difference in overall survival was observed, but there was a trend towards improved survival in both the erlotinib (HR 0.80; 95% CI 0.61-1.05, p=0.13) and gemcitabine (HR 0.81; 95% CI 0.61-1.07, p=0.109) groups in comparison to the observation group. There was no outstanding adverse effect in this group (85).

Four trials evaluated an EGFR TKI as maintenance therapy. There was a clear improvement in PFS, but only one trial showed a significant improvement in overall survival. One Japanese trial compared six cycles of a platinum-doublet with three cycles of a platinum-doublet followed by gefitinib until progression. There was a significant improvement in PFS, but no significant improvement in overall survival (34). A second trial evaluated bevacizumab plus erlotinib with bevacizumab alone in patients treated with four cycles of carboplatin, paclitaxel and bevacizumab. There was a significant improvement in PFS (4.8 months vs 3.7 months, p<0.001) (87). Two additional studies evaluated an EGFR TKI as maintenance therapy compared with a placebo control following four cycles of a platinum-doublet. Both studies showed significant improvements in PFS. The SATURN trial, evaluating maintenance erlotinib, showed a significant improvement in overall survival, although the difference in median survival was only one month (16). In a preplanned subgroup analysis of the SATURN trial, patients with stable disease after first-line chemotherapy had a greater overall survival benefit with maintenance erlotinib (median survival, 11.9 months for erlotinib vs 9.6 months with placebo; HR 0.72; 95% CI 0.59-0.89, p=0.0019) than did patients who had a previous complete or partial response (12.5 months for erlotinib vs 12.0 months for placebo; HR 0.94; 95% CI 0.74-1.20, p=0.618) (16). Zhang et al showed a similar effect on overall survival from maintenance gefitinib, although this difference was not statistically significant (HR 0.84; 95% CI 0.62-1.14) (35).

Quality of life and adverse effects were assessed in two studies (Table 28). The SATURN study showed no statistically significant difference in QoL (FACT–L instrument) for patients receiving erlotinib compared with those receiving placebo (HR 0.96; 95% CI 0.79–1.16 for time to deterioration in quality of life). A post-hoc analysis showed that time to pain (HR 0.61; 95% CI 0.42–0.88, p=0.008) and time to analgesic use (HR 0.66; 95% CI 0.46–0.94, p=0.02) were both significantly improved with erlotinib (16). The Zhang et al study showed that based on the FACT–L questionnaire, median time to worsening of lung cancer symptoms was 4.3 months with gefitinib and 2.3 months with placebo (35).

Adverse effects were consistent with what is expected for gefitinib and erlotinib. There was an increase in rash and diarrhea.

EGFR Inhibitors in Clinically Selected Patients in the Maintenance Setting

One fully published study examined the use of an EGFR inhibitor in clinically selected patients in the maintenance setting. The study characteristics can be seen in Table 29.

This trial randomized 49 patients to gefitinib or pemetrexed making it underpowered to provide meaningful data on efficacy (52). Median PFS showed an HR of 0.191 (95% CI, 0.074-0.0497), and overall survival was prolonged in the pemetrexed and optional-cisplatin group (HR 2.151; 95% CI 0.826-5.599). Adverse effects were consistent with those associated with EGFR inhibitors and chemotherapy (52).

Table 27. EGFR inhibitors versus chemotherapy in unselected patients in the maintenance setting.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate	Median progression-free survival	Median overall survival
Takeda 2010 WJTOG0203 (34) phase 3	Stage IIIB/IV NSCLC; PS 0-1; No prior treatment	Carboplatin AUC6 + paclitaxel 200 mg/m^2 or Cisplatin 80 mg/m^2 + irinotecan 60 mg/m^2 or Cisplatin 80 mg/m^2 + Vinorelbine 25 mg/m^2 or cisplatin 80 mg/m^2 + gemcitabine 1000 mg/m^2 or cisplatin 80 mg/m^2 + docetaxel 60 mg/m^2 and Gefitinib 250 mg/day Above chemo regimen	302/298 301/297	34.2% 29.3 p=0.20	4.6 months 4.3 months HR 0.68; 95% CI 0.57-0.80, p< 0.001	13.7 months 12.9 months
Cappuzzo 2010 (16) SATURN phase 3	Completion of 4 cycles of standard platinum chemotherapy without disease progression PS 0-1 Adequate renal, hepatic and hematological function, negative pregnancy test	Erlotinib 150mg day Placebo	438/437 451/447	11.9% 5.4% p=0.0006	12.3 weeks 6 months 25% (95%CI 21-29) 11.1 weeks HR 0.71; 95%CI 0.62-0.82, p<0.0001 6 months 15% 95% CI 12-19	12 months 11 months HR 0.81; 95% CI 0.70-0.95, p=0.0088
Zhang 2012 (35) phase 3	Stage IIIB/IV NSCLC Completion of 4 cycles of standard platinum chemotherapy without disease progression PS 0-2 Life expectancy of more than 12 weeks Patients with known tumour EGFR status were excluded	Gefitinib 250 mg/day Placebo	148 148	24% 1% OR 54.10 95% CI 7.17-408, p=0.0001	4.8 months 2.6 months HR 0.42; 95% CI 0.33-0.55, p<0.0001	18.7 months 16.9 months HR 0.84; 95% CI 0.62-1.14, p=0.26
Johnson BE 2013 (87) ATLAS phase 2	Stage IIIB/IV NSCLC Completion of 4 cycles of platinum doublet chemotherapy	Erlotinib 150 mg day + Bevacizumab 15 mg/kg Bevacizumab 15mg/kg	370 373	NR	4.8 months 3.7 months HR 0.708; 95% CI:0.580-0.864, p<0.001	14.4 months 13.3 months HR 0.917; 95% CI 0.698-1.205, p=0.5341
Bylicki O 2013 IFCT-GFPC 05-02	Stage IIIB/IV NSCLC PS 0-1 Completion of 4	Erlotinib – 150 mg/day Gemcitabine - 1250mg/m^2	155 154	14% 6%	Between E and O (4.2 vs. 3.9 months, HR 0.83; 95% CI 0.64-1.09	9.1 months 8.3 months

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate	Median progression-free survival	Median overall survival
(85) phase 2	cycles of standard platinum chemotherapy without disease progression	Observation	155	14%	Between G and O (4.2 vs 3.9 months, HR 0.81; 95% CI 0.62-1.06	7.5 months E vs O (HR 0.80; 95% CI 0.61-1.05, p=0.13) G vs O (HR 0.81; 95% CI 0.61-1.07, p=0.109

Table 28. Quality of life and symptom control in EGFR inhibitors in the maintenance setting.

Reference	Treatment	Number enrolled/ analyzed	Quality of life symptom control	Adverse effects
Takeda 2010 WJTOG0203 (34) phase 3	Carboplatin AUC6 + paclitaxel 200 mg/m^2 or Cisplatin 80 mg/m^2 + Irinotecan 60 mg/m^2 or Cisplatin 80 mg/m^2 + Vinorelbine 25mg/m^2 or Cisplatin 80 mg/m^2 + Gemcitabine 1000 mg/m^2 or Cisplatin 80 mg/m^2 + Docetaxel 60mg/m^2 and Gefitinib 250 mg/day Above chemo regimen	302/298 301/297	NR	Grades 3 – 4 (%) G+chemo chemo Anemia 40(13) 65(22) Leucopenia 111(37) 119(40) Neutropenia 38(13) 38(13) Thrombocytopenia 19(6) 32(11) Fatigue 22(7) 29(10) Skin rash 4(14) 2(0.7) Diarrhea 5(1.7) 6(2) Nausea 29(10) 38(13) Vomiting 17(6) 13(4)
Cappuzzo 2010 (16) SATURN phase 3	Erlotinib 150 mg day Placebo	438/437 451/447	There was no statistically significant difference in QoL (FACT-L instrument) for patients receiving Erlotinib compared with those receiving placebo (HR 0.96; 95% CI 0.79–1.16) for time to deterioration in QoL. A post-hoc analysis showed that time to pain (HR 0.61; 95% CI 0.42–0.88, p=0.008) and time to analgesic use (HR 0.66; 95% CI 0.46–0.94, p=0.02) were both significantly improved with Erlotinib vs placebo.	Grades 3 and 4 (%) E P Rash 37(9) 0 Pruritus 1 0 Diarrhea 7(2) 0
Zhang L 2012 (35) phase 3	Gefitinib 250mg/day Placebo	148 148	Based on the FACT –L questionnaire, median time to worsening of lung cancer symptoms was 4.3 months in Gefitinib and 2.3 months with placebo	No grade 3 or 4 adverse effects for rash, pruritus, diarrhea, cough or dyspnea
Johnson BE 2013 (87) ATLAS phase 2	Erlotinib 150 mg day + Bevacizumab 15 mg/kg Bevacizumab 15mg/kg	370 373	NR	Grade 3 & 4 (%) E+B B Rash 25(6.8) 2(0.5) Diarrhea 36(9.8) 7(1.9)

Bylicki 2013 (85) phase 2	Erlotinib – 150 mg/day Gemcitabine - 1250mg/m^2 Observation	155 154 155	NR	Grades 3&4 (%) Anemia Neutro-penia Fatigue	E 5(4.3) 11(9.5) 11(9.5)	G 8(7.0) 22(19.3) 3(2.6)	O 7(5.4) 17(13.1) 14(10.8)

Abbreviation: QoL = Quality of Life.

Table 29. EGFR inhibitor vs chemotherapy in clinically selected patients in the maintenance setting.

Reference	Inclusion criteria	Treatment	Number enrolled/ analyzed	Response rate, CR + PR	Median progression-free survival	Median overall survival	Adverse effects		
Ahn 2012 (52) phase 2	Stage IIIB/IV NSCLC PS 0-1 EGFR mutation status unknown Smoked ≤100 cigarettes in lifetime Life expectancy >12 weeks	Gefitinib 250 mg/day Pemetrexed 500 mg/m^2 + optional cisplatin 75 mg/m^2	25 24	46.2% 35.5% OR 1.56; 95% CI 0.59-4.10, p=0.369	HR 0.191; 95% CI 0.074-0.0497	6 month 80.6% 12 month 74.8% 24 month 59.5% 6 month 93.3% 12 month 93.3% 24 month 77.4% HR 2.151; 95%CI 0.826-5.599	Grades 3 & 4 (%) Neutrophils Vomiting Dyspnea Fatigue Rash	G 1 (4) 0 0 1 (2.6) 2(8)	P 2(8.3) 0 1(4.2) 2(6.5) 0

DISCUSSION

There has been a significant evolution in knowledge about EGFR TKIs since the original version of this guideline was published in 2006 (7). At that time, erlotinib was recommended as second- or third-line therapy for patients who were not candidates for further chemotherapy. These recommendations applied to all patients with NSCLC, as it was not possible to identify a subgroup of patients who failed to benefit from therapy in the NCIC BR21 trial.

Analysis of early trials evaluating EGFR TKIs suggested that clinical characteristics such as Asian ethnicity, female, non-smoker and adenocarcinoma were associated with a higher likelihood of response to EGFR TKIs. These characteristics were used to select patients in subsequent clinical trials to enrich the population who might benefit from these drugs. However, it is now clear that the population of patients who derive the greatest benefit from EGFR TKIs are patients with tumours harbouring activating mutations of the EGFR gene. Nevertheless, the available data still support a more modest benefit from EGFR TKIs in unselected populations of NSCLC patients. This evidence-based summary provides guidance as to the use of EGFR TKI therapy in advanced NSCLC and, in particular, whether there are subpopulations of NSCLC patients in whom the sequence of therapy should be different.

In the first-line setting, there are inconsistent data about the efficacy of EGFR TKIs in comparison to platinum-based chemotherapy. The largest of these trials, TORCH (20), shows statistically significant, inferior overall survival for patients receiving first-line EGFR TKI therapy, and therefore, these agents are not recommended in the first-line setting for an unselected population of NSCLC patients. Studies selecting patients based on clinical characteristics such as Asian ethnicity, smoking status and adenocarcinoma histology also have mixed results. While these strategies are designed to increase the proportion of patients with an EGFR mutation, data from the IPASS trial show that only 60% of patients have EGFR mutations when clinical characteristics are used to select patients (30). Significantly worse response rates and PFS are observed for those patients who are EGFR wild type and treated with first-line gefitinib. Therefore, the use of clinical characteristics such as ethnicity, gender, smoking status, or histology cannot be recommended to select patients for first-line therapy with an EGFR TKI. There are no data to support combining an EGFR TKI with platinum-based chemotherapy.

There is high-quality evidence, though, from multiple randomized clinical trials, that an EGFR TKI is the preferred initial therapy over a platinum-doublet for patients with an activating mutation of the EGFR gene. This is associated with a higher likelihood of response, longer PFS and improved quality of life. There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative. Cohort data from the Spanish Lung Cancer Group (32) report on EGFR TKIs in EGFR-mutated patients given as either first-line or second-line therapy. The benefit appears to be similar in both groups, so that even though it is a non-randomized comparison, the consensus is that cross-over explains the difference. While there is statistical heterogeneity between the trials, there are no data to suggest that one EGFR TKI is superior to another in this setting. Some trials included only exon 19 deletion and exon 21 L858R point mutations, whereas other trials such as Lux-Lung 3 included other less common mutations. This might be a factor for consideration in the choice of agents. However, the decision to use gefitinib, erlotinib or afatinib is largely influenced by concerns about toxicity of the agents, or cost considerations.

Data from the NCIC BR21 trial of erlotinib versus placebo demonstrate a modest improvement in survival and quality of life for erlotinib in patients who are no longer candidates for further chemotherapy (8). Based on these data, erlotinib was recommended as a last line of therapy in the previous version of this guideline. However, there are now multiple trials of second–line therapy comparing an EGFR TKI with chemotherapy. Meta-analysis of these data demonstrates similar PFS and overall survival. Therefore, level-one evidence exists showing there is no preferred sequence for second-line EGFR TKI or second-line chemotherapy. The findings of translational research from the INTEREST study suggests that molecular analyses could not identify a subgroup of patients with improved overall survival from an EGFR TKI or second-line chemotherapy (25). Therefore, it is reasonable to consider an EGFR TKI as either second- or third-line therapy in the treatment of patients with advanced NSCLC. Data from the TAILOR (40) trial, performed only in patients who are EGFR wild type, demonstrated improved PFS and overall survival for patients receiving docetaxel chemotherapy compared with erlotinib. Additionally, the trial did not allow cross-over between the two treatment arms. Therefore, the data does not alter these treatment recommendations at this time. There are inconsistent data concerning the combination of an EGFR TKI with either chemotherapy or another targeted agent. There are some promising data from randomized phase II trials, but these require confirmation in phase III trials. Therefore, combination therapy with an EGFR TKI in the second- or third-line setting is not recommended at this time.

Current data do not support the routine use of an EGFR TKI after disease progression on therapy with another EGFR TKI. While data from the Lux Lung-1 trial demonstrated a significant improvement in PFS in a select subgroup of patients, this trial did not meet its primary objective of improved overall survival (51). Given the absence of improved survival, therapy with afatinib after progression of another EGFR TKI is not recommended.

EGFR TKIs have also been evaluated as a switch-maintenance therapy. The SATURN trial demonstrated improved overall survival in patients receiving maintenance erlotinib (16). Interestingly, this benefit was observed in both patients who were EGFR mutation positive and EGFR wild type. There was no molecular marker that could identify patients in whom a survival benefit was not observed. The magnitude of that benefit was modest, and there are other maintenance therapy strategies that should be considered. Nevertheless, there are data to support maintenance therapy with erlotinib after four cycles of platinum-based chemotherapy.

Lastly, it is evident from this review that determination of EGFR mutation status is essential to make appropriate treatment decisions. Patients who are EGFR-mutation positive should be treated with an EGFR TKI as first-line therapy. An EGFR TKI is still appropriate therapy in patients who are EGFR wild type, but this should be administered as second- or third-line therapy. Programs for EGFR mutation testing need to be in place in order to implement these guideline recommendations. The standard of care in Ontario has now evolved to test for EGFR mutation status up front (114).

CONCLUSIONS

There is an expanded role for therapy with an EGFR TKI since the previous version of this guideline. EGFR TKIs are the preferred initial treatment for patients with EGFR-mutation–positive advanced NSCLC. Data would support the use of gefitinib, erlotinib or afatinib. There is modest benefit from erlotinib as switch-maintenance therapy following four cycles of a platinum-doublet. There are other competing maintenance therapy strategies that should be considered in this setting as well. There is also modest benefit from erlotinib as second- or third-line therapy with an EGFR TKI. Programs for EGFR

mutation testing need to be in place in order to implement these guideline recommendations.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Lung DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Four authors, members and reviewers reported that they had no conflicts of interest. Two others (PE, and RF) declared conflicts and reported receiving more than $5000 in a single year from consulting fees, honoraria and/or other support from Eli Lily, Roche, pharmaceutical companies. One author (PE) also declared that he had received research grant support from Roche and Eli Lily.

Twenty-one members of the Lung DSG members declared they had no conflicts of interest, and five members (SK, RG, NL, MV and SL) declared conflicts. SL, MV and SK reported receiving more than $5000 in a single year. SK reported this was for travel expenses from Roche. MV also received this from Roche. RG and NL have been principal investigators on trials evaluating EGFR inhibitors. MV reported that he has received over $5000 from Roche and Astra Zeneca for consulting. SL reported that he has received income ($5000 or more in a single year) to act in a consulting capacity, has a relevant business entity and stocks, bonds or stock options valuated at $5000 or more in a relevant business entity. SL has also received support for research and been involved in multiple clinical trials using drugs produced by Astra Zeneca and Roche, including erlotinib and gefitinib. He has also published a review article on the role of EGFR TKIs in wild-type NSCLC. In addition, SL has provided guidance or advice regarding EGFR inhibitors in a public capacity and has managerial responsibility for an organization that has received more than $5000 in a single year from a relevant business entity.

The RAP reviewers reported no conflicts of interest.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

ACKNOWLEDGEMENTS

The Lung DSG would like to thank the following participants in the guideline development process:

1. Hans Messersmith, PEBC Assistant Director, Quality and Methods
2. Sheila McNair, PEBC Assistant Director, Business Operations
3. Carol De Vito, Documents Manager
4. Hawkanwal Randhawal and Jagpreet Kaler for conducting the Data Audit
5. Internal Peer Reviewers, Glenn Fletcher and Xiaomei Yao

For a complete list of the Lung DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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gemcitabine compared to gemcitabine monotherapy as first-line therapy in elderly or ECOG PS of 2 patients with advanced NSCLC. J Thorac Oncol. 2012;3:S177-S8.
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Appendix A: Literature Searches.

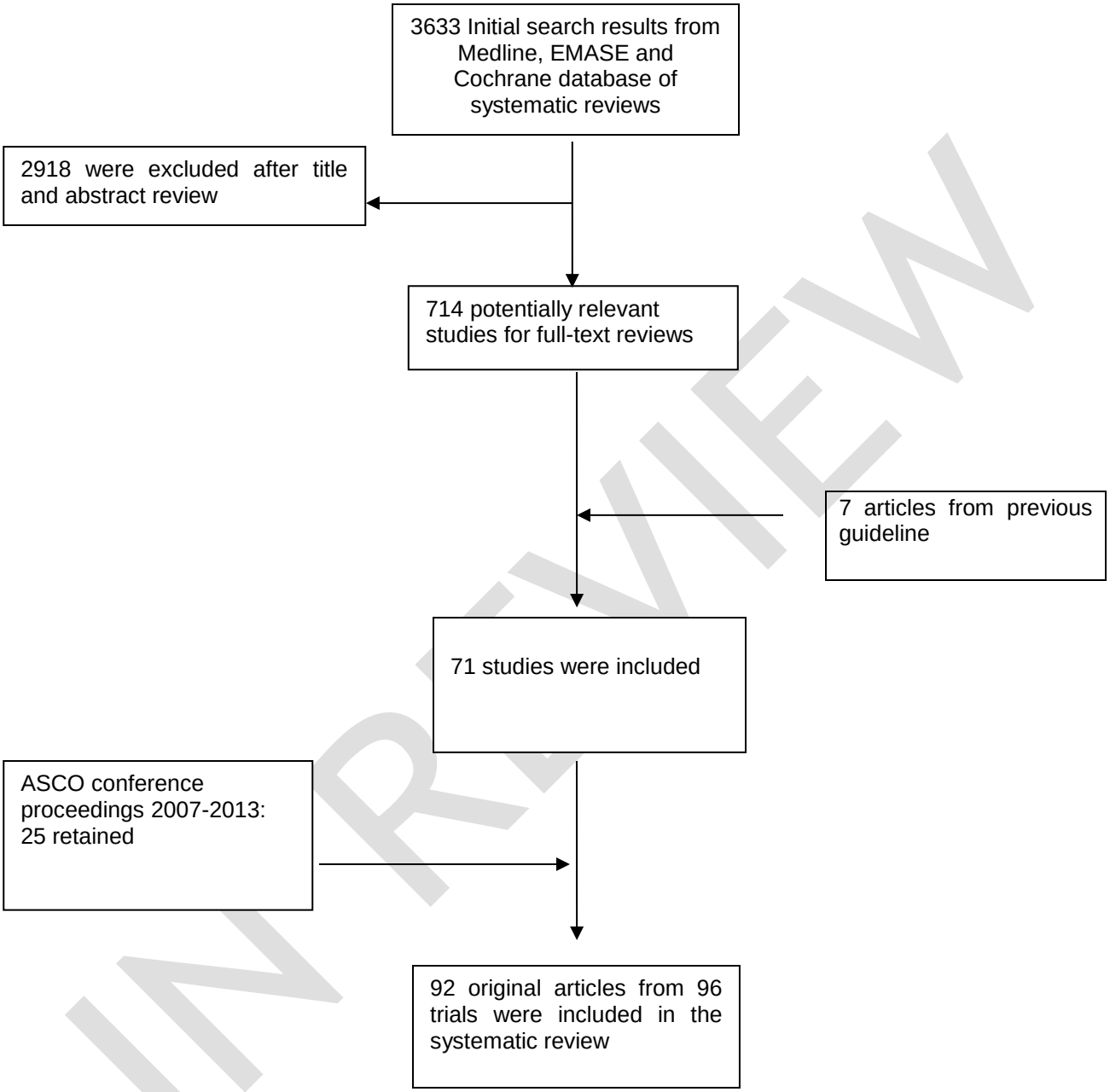
MEDLINE

1. practice guidelines/
2. practice guideline.pt.
3. practice guideline?.tw.
4. practice guideline?.mp.
5. systematic review?.mp.
6. systematic overview?.mp.
7. Meta-analysis/
8. meta analysis.pt.
9. metaanalys$.mp.
10. meta analys$.mp.
11. metaanal$.mp.
12. random$.mp.
13. randomized controlled trials/
14. randomized controlled trial.pt.
15. randomised controlled trial.mp.
16. controlled clinical trials/
17. controlled clinical trial.pt.
18. random allocation/
19. clinical trials/
20. (random$ and (trial$ or stud$)).mp.
21. quantitative overview?.mp.
22. quantitative review?.mp.
23. or/1-22
24. exp lung neoplasm/ or carcinoma, non-small-cell lung/
25. NSCLC.mp.
26. (lung and (cancer$ or neoplasm$ or carcinoma$ malignan$ or tomo?r$)).mp.
27. non small cell lung.mp.
28. (lung adj3 (cancer? or carcinoma?)).mp.
29. or/24-28
30. 23 and 29
31. iressa.mp.
32. Gefitinib.mp.
33. tarceva.mp.
34. Erlotinib.mp.
35. afatinib.mp.
36. tomtovok.mp.
37. tovok.mp.
38. Bibw2992.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, ps, rs, an, ui]
39. bibw 2992.mp.
40. bibw-2992.mp.
41. dacomitinib.mp.
42. "PF 00299804".mp.
43. pf-00299804.mp.
44. icotinib.mp.
45. BPI-2009h.mp.
46. bpi 2009h.mp.
47. or/31-46
48. 30 and 47
49. limit 48 to yr="2006 -Current"

EMBASE

1. exp lung carcinogenesis/ or exp lung adenocarcinoma/ or exp lung alveolus cell carcinoma/ or exp lung non small cell cancer/ or exp lung squamous cell carcinoma/
2. non small cell lung.tw.
3. (lung adj3 (cancer? or carcinoma?)).tw.
4. or/1-3
5. exp Erlotinib/ or Gefitinib/
6. exp epidermal growth factor receptor/
7. iressa.tw.
8. Gefitinib.tw.
9. zd1839.tw.
10. zd 1839.tw.
11. tarceva.tw.
12. Erlotinib.tw.
13. osi 774.tw.
14. osi774.tw.
15. afatinib.tw.
16. tomtovok. tw.
17. tovok. tw.
18. Bibw2992. Tw.
19. bibw 2992. tw.
20. bibw-2992. tw.
21. dacomitinib. tw.
22. "PF 00299804". tw.
23. pf-00299804. tw.
24. icotinib. tw.
25. BPI-2009h. tw.
26. bpi 2009h. tw
27. or/5-46
28. 4 and 15
29. exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp randomized controlled trial/ or methodology/ or exp cohort analysis/ or exp double blind procedure/ or exp single blind procedure/ or exp meta analysis/ or exp practice guideline/
30. (random: adj3 (trial or study)).tw.
31. (systematic adj3 (review or overview)).tw.
32. (quantitative adj3 (review or overview or synthesis or syntheses)).tw.
33. meta-anal:.tw.
34. metaanal:.tw.
35. metanal:.tw.
36. or/29-35
37. 28 and 35
38. limit 37 to yr="2005 -Current"

Appendix B: Literature Search flow diagram.



Appendix C: Study quality table for fully published studies.

Study	Phase	Funding	Methods of randomization	Allocation concealment	Patient stratification	Power reported	Cross-over after progression	ITT
Aerts JG 2013 (82)	2	Cooperative group	x	Open label	Response to prior treatment, PS and histology	x		Not stated
Ahn MJ 2012 (52)	2	Industry	x		Tumour histology and gender	x		x
Besse B 2014 (84)	2	Industry		Open label	Smoking history, and histology	x		No
Belani	2	Industry		Open label	PS smoking history	x		No
Boutsikou E 2013(39)	3	Not stated		Open label	Not stated	x		Not stated
Bylicki O 2013 (85)	3	Cooperative group			Centre, gender, histology, smoking status response to induction treatment	Not stated		Not stated
Cappuzzo F SATURN 2010 (16)	3	Industry	x		EGFR status, stage, PS, chemo regimen, smoking history, geographic region	x		x
Chen YM 2007 (55)	2	Not stated				x		x
Chen YM 2011 (54)	2	Government grant			Gender and smoking history	x		x
Chen YM 2012 (53)	2	Industry		Open label	Histology, smoking status, ECOG PS, and gender	x		x
Ciuleanu T TITAN 2012 (17)	3	Industry	x	Open label	Stage of disease at start of Treatment, ecog ps, smoking history and region of residence	x		x
Crino L 2008 INVITE (56)	2	Industry		Open label		x		x
Cufer T SIGN 2006 (57)	2	Industry	x	Open label		x (not enough)		x
Fukuoka M 2003 IDEAL (58)	2	Industry	x	Double blind	Ethnicity	x		x
Gaafar RM EORTC 0821/(18) ILCP 01/03 2011	3	Industry		Double blind	Stage, PS after chemo, best response and institution	x		x
Garassino MC 2013 (40)	3	Government agency	x		Centre, stage, type of 1st line chemotherapy and PS	x		Not stated
Gatzemeier U 2007 (19)	3	Industry				x	x	no

Study	Phase	Funding	Methods of randomization	Allocation concealment	Patient stratification	Power reported	Cross-over after progression	ITT
Giaccone G INTACT1 2004(38)	3	Industry	x	Double blind	Weight loss in previous 6 months, stage, PS and measurable disease	x		x
Goss G 2009 (59)	2	Industry				x		x
Gridelli C 2011 (60)	2	Cooperative group				No		not stated
Gridelli C TORCH 2012 (20)	3	Industry	X		Histology, smoking status, sex, age, centre, and PS	x		x
Groen HJM 2013(86)	2	Industry	X	Blinding	Smoking history, and EGFR status	X		x
Han JH 2011 (61)	2	Government grant		Open label	Gender, PS, prior regimens	x		x
Han JY FirstSIGNAL 2012 (21)	3	Cooperative group and industry		Open label, blinded radiologist	Gender, PS stage	x		not stated
Herbst RS INTACT 2 2004(22)	3	Industry			Weight loss in previous 6 months, stage, PS and presence of measureable disease	x		x
Herbst RS TRIBUTE 2005(23)	3	Cooperative group			Disease stage, weight loss during the past 6 months, tumour measurability and treatment centre	x		x
Herbst RS 2007 (62)	2	Industry			PS smoking history	x (not enough)	x	not stated
Herbst RS BeTa 2011 (24)	3	Industry	x	Double blind	Gender, PS, smoking history, centre	x		x
Hirsch FR 2011 (63)	2	Industry	x		Positive EGFR tests, smoking status, PS, stage IIIB or IV	x (not enough)		No
Janne PA CALGB 2012 (64)	2	Cooperative group				x		
Johnson BE 2013 (87)	3	Industry	x	Open label	Gender, smoking history, PS and initial chemotherapy regimen	X		X
Karampeazis A 2013 (41)	3	Grant	x	Open label	PS, stage and response to first line treatment	x	x	x
Kelly KC 2012 (65)	2	Industry			Degree of smoking	x (not enough)		x

Study	Phase	Funding	Methods of randomization	Allocation concealment	Patient stratification	Power reported	Cross-over after progression	ITT
Kim ES INTEREST 2008 (25)	3	Industry	x	Open label	Histology, PS, previous chemo, number of previous regimens, smoking history, study site	not stated		both
Kim S.T. 2012 (66)	2	Grant	x		EGFR mutation versus at least Two among three factors: female-gender, adenocarcinoma histology, and never-smoker	x		x
Kris MG 2003 (67)	2	Industry		Double blind	PS, and number of prior chemo regimens	x		Not stated
LeCaer H GFP 0504 2011 (68)	2	Industry		Open label		x		No
LeCaer H GFPC 2012 (69)	2	Industry		Open label		x		x
Lee DH ISTANA 2010 (26)	3	Industry		Open label	Histology, gender, PS, best response to previous therapy, smoking history, centre	x		x
Lee DH 2013(88)	2	Industry	x	Open label	PS and histology	x		x
Lee SM 2012 TOPICAL (42)	3	Grant and industry	x	Double blind	Stage, PS, smoking history, and centre	x		Not stated
Lilenbaum R 2008(70)	2	Industry			Centre, stage, age	x	x	No
Lynch TJ 2009 (71)	2	Industry		Open label	Histology, smoking history, gender	x		x
Maemondo M 2010 (27)	3	Government grant			Gender, stage, centre	x		x
Maruyama R V-15-32 2008 (28)	3	Industry			Gender, PS histology, study site	x		x
Miller VA LUX-Lung1 2012 (51)	2b/3	Industry	x	Double blind	Gender and ECOG baseline	x		x
Mitsudomi T WJTOG 3405 2010 (29)	3	Cooperative group and industry	x	Open label	Centre, adjuvant therapy, interval between surgery, gender and stage	x		x
Mok TSK 2009 (30)	3	Industry		Open label		x		x
Mok TSK 2009 IPASS (72)	2	Industry	x		Centre, stage iiib/iv, smoking status		x	not stated

Study	Phase	Funding	Methods of randomization	Allocation concealment	Patient stratification	Power reported	Cross-over after progression	ITT
Morere JF. IFCT-0301 2010 (73)	2	Industry	x			x	x	No
Natale RB 2009 (74)	2	Industry				x		x
Natale RB 2011 (31)	3	Industry		Double blind		x		x
Ramalingam SS 2011 (76)	2	Industry		Open label/blinded manner		x		x
Ramalingam SS 2012 (75)	2	Industry			Smoking status, race, and histologic subtype	x		x
Riley GJ 2009 (77)	2	Industry				x		not stated
Rosell RE EURTAC 2012 (32)	3	Cooperative group and industry	x	Open label	Type of EGFR mutations, and PS	x		x
Scagliotti GV 2012 (33)	3	Industry	x	Triple blind	Smoking history, prior bevacizumab, and EGFR status	x		x
Sequist LV 2011 (78)	2	Industry			Gender, age, smoking status, histology, PS, prior chemo, best response to chemo and study site	x		x
Shepherd FA 2005 BR21 (8)	3	Cooperative group	x	Double-blind	Centre, PS, best response to prior therapy, number of prior regimens and exposure to platinum therapy	x		x
Shi Y 2013(43)	3	Industry	x		Histology, smoking status and PS	x		Not stated
Spigel DR 2011 (79)	2	Industry			Histology. Exposure to bevacizumab	x		No
Spigel DR 2013 (89)	2	Industry	x	Double blind	Smoking status, PS and histology	Not stated		x
Stinchcombe TE 2011 (80)	2	government grant			Gender smoking status, PS	x	x	x
Takeda K WJTOG020 2010 (34)	3	Cooperative group and industry			Centre, histology, stage, platinum doublet regimens	x		no
Thatcher N 2005 ISEL(37)	3	industry	x	Double -blind	Histology, smoking status, reasons for previous chemo failure, number of previous	x		x

Study	Phase	Funding	Methods of randomization	Allocation concealment	Patient stratification	Power reported	Cross-over after progression	ITT
					chemo regimens, PS, and gender			
Witta SE 2012 (81)	2	Industry	x	Blinded	Smoking status	x		x
Wu Y-L 2013 Lux-Lung 6 (44)	3	Industry	X		EGFR mutation	x		x
Zhang L 2012 (35)	3	Industry	x	Double blind	Histology, smoking history	x		x
Zhou C OPTIMAL CTONG-0802 2011 (36)	3	Industry	x	Open label	Mutation type, histological subtype, smoking status	x		no

Appendix D: Ongoing trials.

Protocol ID	Study details
Gefitinib	
Paclitaxel/Carboplatin (PC) Followed by Gefitinib Versus PC in Advanced Non-small Cell Lung Cancer (PRIDE) NCT01196234	A randomized phase II trial that compares paclitaxel/carboplatin (PC) to PC chemotherapy followed by Gefitinib for 2 weeks in patients with NSCLC without EGFR mutations. While previous studies with cytotoxic agents and Gefitinib failed to show any benefit, we altered the schedule of administration in hopes to gain synergy between agents.
Study of Pemetrexed Versus Gefitinib in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Previously Received Platinum-Based Chemotherapy Without Epidermal Growth Factor Receptor (EGFR) Mutations NCT00891579	This study is a prospective trial of Alimta (pemetrexed) versus IRESSA (Gefitinib) among epidermal growth factor receptor wild-type non-small-cell lung cancer (NSCLC) patients in a 2nd-line setting.
Phase II Study of Gefitinib Plus Nimotuzumab Versus Gefitinib in Non-small Cell Lung Cancer (DATE) NCT01498562	Combining nimotuzumab to Gefitinib may not only potentiate cellular cytotoxicity, but may also assist in overcoming inherent or acquired resistance to Gefitinib alone.
A Study of Pemetrexed and Gefitinib Versus Gefitinib in Non-Small Cell Lung Cancer (NSCLC) NCT01469000	The purpose of this study is to compare the combination of pemetrexed and Gefitinib versus Gefitinib alone, in terms of progression-free survival. This study is in participants who have stage IV non-squamous NSCLC with activating epidermal growth factor mutations and who have not had any previous chemotherapy for stage IV disease.
Paclitaxel, Carboplatin, and Gefitinib in Treating Patients With Advanced Non-Small Cell Lung Cancer NCT01024712	This phase II trial is studying the side effects of giving paclitaxel and carboplatin together with Gefitinib and to see how well it works in treating patients with Stage IIIB or stage IV non-small-cell lung cancer.
A Study of IRESSA Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone (IMPRESS) NCT01544179	The purpose of this study is to assess the efficacy and safety of Gefitinib in patients who have progressed on first-line Gefitinib, comparing continuing Gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.
Study of Gefitinib Compared With Pemetrexed/Cisplatin in Advanced Non-Small Cell Lung Cancer Patients NCT01192243	The purpose of this study is to examine the efficacy and safety of Gefitinib combined with Pemetrexed/Cisplatin in advanced non-small-cell lung cancer (NSCLC).
Erlotinib Versus Gefitinib in Advanced Non Small Cell Lung Cancer With exon21 Mutation : A Randomized Trial NCT01024413	This is a randomized open-label controlled phase II trial comparing efficacy of Erlotinib and Gefitinib in patients with exon21 mutation advanced NSCLC as a first-line treatment setting.
Intercalated Administration of PamCis With Gefitinib or Placebo as First Line Lung Adenocarcinoma in Never Smokers NCT01502202	Intercalated administration of Iressa® (Gefitinib) on days 5-18 of chemotherapy cycle improve the efficacy of Pemetrexed/platinum regimen given as first-line treatment for never smokers with advanced (stage IIIB/IV) lung adenocarcinoma.
Erlotinib	
Study of Erlotinib (Tarceva®) in Combination With OSI-906 in Patients With Advanced Non-small Cell Lung Cancer (NSCLC) With Activating Mutations of the Epidermal Growth Factor Receptor (EGFR) Gene NCT01221077	This is a multi-centre, randomized (1:1), double-blind, placebo-controlled, phase 2 study. Patients will be stratified according to the following 2 parameters: (1) EGFR activating mutation type (exon 19 deletion versus exon 21 single point mutation); and (2) Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1).

Protocol ID	Study details
Randomized Phase II Study of AZD6244 MEK-Inhibitor With Erlotinib in KRAS Wild Type and KRAS Mutant Advanced Non-Small Cell Lung Cancer NCT01229150	To determine the effectiveness of AZD6244, either alone or in combination with Erlotinib, in preventing tumour growth in individuals with NSCLC.
Erlotinib With or Without Hydroxychloroquine in Chemo-Naive Advanced NSCLC and (EGFR) Mutations NCT00977470	The purpose of this research study is to learn if adding hydroxychloroquine (HCQ) to Erlotinib helps treat non-small-cell lung cancer (NSCLC). Another goal of this research study is to learn more about NSCLC and how it may respond to study treatment.
Erlotinib Plus ARQ 197 Versus Single Agent Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer NCT01395758	The purpose of this study is to evaluate progression-free survival among subjects with KRAS mutation positive non-small-cCell lung cancer (NSCLC) treated with Erlotinib plus ARQ 197 compared to single-agent chemotherapy.
2nd Line Erlotinib Treatment With (Out) Chemotherapy of Advanced Non Small Cell Lung Cancer (NSCLC) (NVALT10) NCT00835471	The purpose of this study is to assess if the combination of Erlotinib and chemotherapy (docetaxel in case of squamous cell NSCLC or pemetrexed in case of other histological types) is superior to Erlotinib alone and has acceptable tolerability and safety in the 2nd-line treatment of patients with advanced/metastatic non-small-cell lung cancer (NSCLC).
Erlotinib Versus Carboplatin/Vinorelbine in Elderly Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) (TIE) NCT00678964	Therefore, the aim of this study is to investigate the progression-free survival of the combination of vinorelbine and carboplatin in comparison to Erlotinib. Given that there will be no significant reduction of efficiency, this may provide elderly patients of more than 70 years of age with an active oral substance without subjecting them to the sometimes severe adverse effect of the chemotherapy.
Erlotinib Versus Gemcitabine/Cisplatin as (Neo)Adjuvant Treatment in Non-small Cell Lung Cancer (EMERGING) NCT01407822	The aim of this study is to investigate the efficacy and safety of Erlotinib versus GEM plus cisplatin (GC) as neoadjuvant treatment in patients with stage IIIA-N2 NSCLC with EGFR activating mutations and to explore a new treatment strategy for this subset.
Erlotinib and Docetaxel in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) After Failure of One Chemotherapy Regimen NCT00908336	This study will investigate if the intermittent treatment of a chemotherapy drug, such as docetaxel, with Erlotinib could achieve a clinical benefit.
Erlotinib With or Without Carboplatin and Paclitaxel in Treating Patients With Stage IIIB or Stage IV Non-Small Cell Lung Cancer NCT00661193	This randomized phase II trial is studying how well Erlotinib works when given alone or together with carboplatin and paclitaxel in treating patients with stage IIIB or stage IV non-small-cell lung cancer.
Erlotinib With or Without Bevacizumab in Treating Patients With Stage IV Non-Small Cell Lung Cancer With EGFR Mutations NCT01532089	This randomized phase II trial studies how well giving erlotinib (Tarceva) with or without bevacizumab (Avastin) works in treating patients with stage IV non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.
Phase III Study (Tarceva®) vs. Chemotherapy to Treat Advanced Non-Small Cell Lung Cancer (NSCLC) in Patients With Mutations in the TK Domain of EGFR NCT00446225	A Phase III, multicentre, open-label, randomized trial of erlotinib (Tarceva) versus chemotherapy in patients with advanced NSCLC with mutations in the Tyrosine Kinase (TK) domain of the EGFR.

Protocol ID	Study details
Erlotinib With or Without Fulvestrant in Treating Patients With Stage IIIB or Stage IV Non-Small Cell Lung Cancer NCT00100854	This randomized phase II trial is studying giving Erlotinib together with fulvestrant to see how well it works compared to Erlotinib alone in treating patients with stage IIIB or stage IV non-small cell lung cancer.
ARCHER 1009 : A Study Of PF-00299804 (Dacomitinib) Vs. Erlotinib In The Treatment Of Advanced Non-Small Cell Lung Cancer NCT01360554	This is a multinational, multicenter, randomized, double-blinded, Phase 3 study comparing the efficacy and safety of treatment with PF-00299804 to treatment with Erlotinib in patients with advanced non-small cell lung cancer, previously treated with at least one prior regimen. Analyses of primary objective (Progression Free Survival) will be done in two co-primary populations as defined in the protocol.
A Study of Tarceva (Erlotinib) to Compare Two Different Doses in in Currently Smoking Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (CURRENTS) NCT01183858	This prospective, double-blind, randomized study will evaluate the safety and efficacy of two dose levels of Erlotinib [Tarceva] on progression-free survival, response and disease control rates and overall survival in patients with advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of first-line platinum-based chemotherapy. Patients must be current smokers and not intending to stop smoking during the study.
Erlotinib Versus Carboplatin/Vinorelbine in Elderly Patients With Advanced Non-small-cell Lung Cancer (NSCLC) (TIE) NCT00678964	Therefore, the aim of this study is to investigate the progression-free survival of the combination of vinorelbine and carboplatin in comparison to Erlotinib. Given that there will be no significant reduction of efficiency this may provide elderly patients of more than 70 years of age with an active oral substance without subjecting them to the sometimes severe adverse effect of the chemotherapy.
A Study of Erlotinib [Tarceva] as Monotherapy or Intermittent Dosing With Docetaxel in Patients With Advanced or Metastatic Non-small-cell Lung Cancer. (TALISMAN) NCT01204697	This randomized parallel group study will assess the efficacy and safety of Erlotinib [Tarceva], as monotherapy or intermittent dosing with docetaxel, in second-line setting in former-smoker male patients with advanced or metastatic squamous non-small-cell lung cancer.
MET/VEGFR2 Inhibitor GSK1363089 and Erlotinib Hydrochloride or Erlotinib Hydrochloride Alone in Treating Patients With Locally Advanced or Metastatic Non-small-cell Lung Cancer That Has Not Responded to Previous Chemotherapy NCT01068587	This randomized phase I/II trial is studying the side effects of Erlotinib hydrochloride when given together with or without MET/VEGFR2 inhibitor Foretinib and to see how well it works in treating patients with locally advanced or metastatic non-small-cell lung cancer that has not responded to previous chemotherapy.
Pemetrexed or Docetaxel With or Without Erlotinib in Stage IIIB or Stage IV Non-small-cell Lung Cancer NCT00660816	This randomized phase II trial is studying how well giving pemetrexed disodium or docetaxel together with or without Erlotinib hydrochloride works in treating patients with stage IIIB or stage IV non-small-cell lung cancer.
A Study of Tarceva (Erlotinib) Versus Gemcitabine/Cisplatin as First-Line Treatment in Patients With Non-small-cell Lung Cancer With EGFR Mutations NCT01342965	This open-label, randomized, parallel arm study will assess the efficacy and safety of Tarceva (Erlotinib) versus gemcitabine/cisplatin combination chemotherapy as first-line treatment in patients with stage IIIB/IV non-small-cell lung cancer with EGFR mutations in their tumours.
Erlotinib and Docetaxel in Second Line of Treatment in Patients With Non Small Cell Lung Cancer (TARSEQ) NCT01350817	The main of this study is to determine the relevance of the association sequential Erlotinib and docetaxel in terms of progression-free survival.
Influence of Prior Chemotherapy on Clinical Benefit	To compare the differential influence of 1st-line doublet chemotherapy containing Docetaxel

Protocol ID	Study details
With Erlotinib in Patients With Advanced Non-Squamous Non-small-cell Lung Cancer With or Without EGFR Gene Mutation NCT01204307	versus Pemetrexed on clinical efficacy of Erlotinib as a second-line therapy in patients with relapsed or progressed non-squamous NSCLC.
A Study of Onartuzumab (MetMAb) in Combination With Tarceva (Erlotinib) in Patients With Met Diagnostic-Positive Non-small-cell Lung Cancer Who Have Received Chemotherapy For Advanced or Metastatic Disease (MetLung) NCT01456325	This randomized, multicentre, double-blind, placebo-controlled study will evaluate the efficacy and safety of onartuzumab (MetMAb) in combination with Tarceva (Erlotinib) in patients with incurable non-small-cell lung cancer identified to be Met diagnostic-positive. Patients will be randomized to receive either onartuzumab (MetMAb) or placebo in combination with Tarceva.
KD019 Versus Erlotinib in Subjects With Stage IIIB/IV Non Small Cell Lung Cancer With Progression After First- or Second-Line Chemotherapy NCT01487174	This study involves treatment with KD019 or Erlotinib in patients with non-small-cell lung cancer (NSCLC) who have progressed after first- or second-line chemotherapy. It is hypothesized that KD019 can prolong survival compared with Erlotinib.
BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-small-cell Lung Cancer NCT01248247	The goal of this clinical research study is to learn if drug or drug combinations based on your biomarkers can help to control NSCLC. The safety of these drug combinations will also be studied.
Erlotinib Versus Gefitinib in Advanced Non Small Cell Lung Cancer With exon21 MutationA Randomized Trial NCT01024413	This is a randomized open-label controlled phase II trial comparing efficacy of Erlotinib and Gefitinib in patients with exon21 mutation advanced NSCLC as a first-line treatment setting.
A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study of ARQ 197 Plus Erlotinib Versus Placebo Plus Erlotinib (ATTENTION) NCT01377376	The primary objective of this study is to determine if the combination regimen of ARQ 197 with Erlotinib will improve overall survival (OS) compared to Erlotinib monotherapy in subjects with locally advanced or metastatic non-squamous NSCLC with wild-type EGFR who have received 1 or 2 prior systemic anti-cancer therapies in the Intent-to-Treat (ITT) population.
Testing of Drugs Erlotinib and Docetaxel in Lung Cancer Patients Classified Regarding Their Outlook Using VeriStrat®. (EMPHASIS) NCT01652469	Using a laboratory test (VeriStrat), patients with relapsed squamous cell lung cancer are assigned to two strata, VSG (VeriStrat Good) and VSP (VeriStrat Poor). They are then randomized between an EGFR-TK inhibitor (Erlotinib) and chemotherapy (Docetaxel). It is hypothesized that the VeriStrat test results are able to predict the benefit of treatment with Erlotinib vs. docetaxel. This would suggest a significant improvement in progression-free survival for VSG patients when treated with Erlotinib, and no significant improvement in VSP patients who receive the same treatment.
Pemetrexed or Erlotinib as Second-Line Therapy in Treating Patients With EGFR Wild-type Advanced Lung Adenocarcinoma NCT01565538	Therefore, we investigate the efficacy of pemetrexed and Erlotinib as second-line therapy in treating in patients with EGFR wild-type advanced lung adenocarcinoma.

Protocol ID	Study details
LUX-Lung 8: A Phase III Trial of Afatinib (BIBW 2992) Versus Erlotinib for the Treatment of Squamous Cell Lung Cancer After at Least One Prior Platinum Based Chemotherapy NCT01523587	This randomised, open-label phase III trial will be performed in patients with advanced squamous cell carcinoma of the lung requiring second-line treatment after receiving first-line platinum-based chemotherapy. The primary objective of this trial is to compare the efficacy of BIBW 2992 to Erlotinib as second-line treatment in this group of patients.
LUX-Lung 7: A Phase IIb Trial of Afatinib(BIBW2992) Versus Gefitinib for the Treatment of 1st Line EGFR Mutation Positive Adenocarcinoma of the Lung NCT01466660	This is a randomised, open-label, phase IIb trial of afatinib to compare to Gefitinib in first-line treatment setting with patients who are having epidermal growth factor receptor mutation-positive advanced adenocarcinoma of the lung.
LUX-Lung 5: Afatinib Plus Weekly Paclitaxel Versus Investigator's Choice of Single Agent Chemotherapy Following Afatinib Monotherapy in Non-small-cell Lung Cancer Patients Failing Erlotinib or Gefitinib NCT01085136	The primary objective of this randomized, open-label, active-controlled, multi-centre trial is to determine the efficacy of BIBW 2992 given as an add-on to chemotherapy in patients with NSCLC Stage IIIb or IV progressing after BIBW 2992 monotherapy compared to chemotherapy alone in this patient population. Patients on both treatment arms will receive best supportive care in addition to study treatment. Patients enrolled into the trial will be treated and followed until death or lost to follow-up. Additional information on the health-related quality of life (HRQOL) will be collected.
BIBW 2992 (Afatinib) vs. Gemcitabine-cisplatin in 1st Line Non-small-cell Lung Cancer (NSCLC) NCT01121393	To compare the efficacy of single agent BIBW 2992 with Gemcitabine&Cisplatin chemotherapy as first line treatment for lung adenocarcinoma with tumour harboring an EGFR activating mutation
BIBW 2992 Plus Simvastatin vs. BIBW 2992 in Previously Treated Patients With Advanced Non-adenocarcinomatous NSCLC NCT01156545	The investigators hypothesized that simvastatin may enhance sensitivity to BIBW 2992 in non-adenocarcinoma that is relatively resistant to TKIs. Based on these data, the investigators will research the effectiveness comparing BIBW2992, an irreversible EGFR-TKI, plus simvastatin with BIBW2992 alone in the setting of a randomized phase II study in previously treated patients with advanced non-adenocarcinomatous non-small-cell lung cancer (NSCLC).
BIBW 2992 (Afatinib) Versus Chemotherapy as First Line Treatment in NSCLC With EGFR Mutation NCT00949650	This randomised, open label phase III trial will be performed in patients with adenocarcinoma of the lung with tumours harbouring an Epidermal Growth Factor Receptor activating mutation. The objectives of the trial are to compare the efficacy of single agent BIBW 2992, Arm A, with Pemetrexed/Cisplatin chemotherapy, Arm B, as first-line treatment for this group of patients.
Concise vs. Prolonged Afatinib in NSCLC With EGFR Mutation NCT01746251	This research study is a phase II clinical trial, which tests the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific cancer. "Investigational" means that the drug is still being studied. It also means that the FDA has not yet approved afatinib for use in patients. In this research study, the investigators are looking to see if taking afatinib after surgery works better when taken over a short period of time, compared to a long period of time.
Icotinib at Different Doses in Second-line Treatment for Non-small-cell Lung Cancer Patients With Wild Type EGFR NCT01744925	This study is designed to evaluate the safety and efficacy of icotinib at routine dose and higher dose as second-line treatment in non-small-cell lung cancer patients with epidermal growth factor receptor of wild type.
Dose Escalation of Icotinib in Advanced Non-small-cell Lung Carcinoma (NSCLC) Patients Evaluated as Stable Disease NCT01690390	The primary purposes of this study are to assess the safety and efficacy of using high doses of the drug Icotinib (Comana) as a way to treat patients with non-small-cell lung cancer that achieve stable disease after 8 weeks routine therapy.
Icotinib in Combination With Chemotherapy Versus Chemotherapy Alone in Patients Progressed After Icotinib	This phase II randomised, double blind, placebo controlled, multicentre trial is designed to assess the efficacy and safety of continuous icotinib plus chemotherapy versus chemotherapy alone in

Protocol ID	Study details
Treatment NCT01707329	patients who have progressed after benefiting from previous second- or third-line icotinib treatment (more than 6 months) in locally advanced or metastatic non-small-cell lung cancer.
Maintenance	
Genius Study to Compare Efficacy and Safety of Gefitinib/ Pemetrexed With Pemetrexed Alone as Maintenance Therapy in Patients With Stage IV EGFR Mutation Negative or T790M Single Mutation Who Respond to Pemetrexed/ Platinum as First-line Therapy NCT01579630	The study aims to randomize 122 patients with advanced (Stage IV) EGFR mutation negative nonsquamous non-small-cell lung cancer (NSCLC) who respond (CR/PR/SD) to 4 cycles of pemetrexed / cisplatin or pemetrexed/carboplatin as first-line therapy. In order to achieve that, approximately 338 treatment naive patients with advanced non-squamous NSCLC need to be enrolled from around 5-7 investigational sites in Taiwan that have expertise in lung cancer diagnosis.
Study of First-line Maintenance Tarceva (Erlotinib) Versus Tarceva at Time of Disease Progression in Patients With Advanced Non-small-cell Lung Cancer After Chemotherapy NCT01328951	This double-blind, placebo-controlled study will evaluate the benefit of first-line maintenance Tarceva (Erlotinib) versus Tarceva at the time of disease progression in patients with advanced non-small-cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum based-chemotherapy and whose tumour does not harbour an EGFR activating mutation. Patients will be randomized to receive either Tarceva 150 mg orally daily or placebo until disease progression or unacceptable toxicity occurs. Patients who progressed on placebo will receive Tarceva 150 mg orally daily in second line until disease progression or unacceptable toxicity. Anticipated time on study treatment is up to 42 months.
Phase 2 Study of Maintenance OSI-906 Plus Erlotinib (Tarceva®), or Placebo Plus Erlotinib in Patients With Nonprogression Following 4 Cycles of Platinum-based Chemotherapy NCT01186861	A multicentre, randomized, double-blind, placebo-controlled, phase II study with a 1:1 randomization scheme.
Phase IIB/III Of TG4010 Immunotherapy In Patients With Stage IV Non-small-cell Lung Cancer (TIME) NCT01383148	This is a phase IIb/III randomized, double-blind, placebo-controlled study to compare the efficacy and safety of first-line therapy combined with TG4010 or placebo in stage IV non-small-cell lung cancer (NSCLC). TG4010 is a suspension of recombinant Modified Vaccinia virus strain Ankara (MVA strain) carrying coding sequences for human MUC1 antigen and human interleukin-2 (IL2). TG4010 has been developed for use as an immunotherapy in cancer patients whose tumours express the MUC1 antigen.
Icotinib as First-line and Maintenance Treatment in EGFR Mutated Patients With Lung Adenocarcinoma NCT01665417	This study is designed to compare the efficacy and safety of first-line icotinib treatment and first-line chemotherapy followed by maintenance treatment with icotinib.
Icotinib Versus First-line Chemotherapy Plus Maintenance Treatment in EGFR Positive Lung Adenocarcinoma Patients (Convince) NCT01719536	The purpose of this study is to compare icotinib with induction and maintenance chemotherapy in the first-line treatment of advanced non-small-cell lung cancer (NSCLC) patients with EGFR mutation.
PF-00299804 in Treating Patients With Stage IIIB or Stage IV Non-small-cell Lung Cancer That Has Not Responded to Standard Therapy for Advanced or Metastatic Cancer NCT01000025	This randomized phase III trial is studying PF-00299804 to see how well it works compared with a placebo in treating patients with stage IIIB or stage IV non-small-cell lung cancer that has not responded to standard therapy for advanced or metastatic cancer.

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline:

Development Methods, Recommendations Development, and External Review Process

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung and the Lung DSG.

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 8, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its

interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following:

1. Comments were made that the wording of the research questions and recommendations should be clarified.
   Response: The wording of the research questions and recommendations has been changed.

2. A comment was made about the wording of the questions differing slightly between sections.
   Response: This has been changed in the document.

3. A comment was made about defining what advanced NSCLC.
   Response: This has been changed in the document.

4. A comment was made about using phase II randomized trials.
   Response: The working group decided a priori to include all phase III and II randomized trials so that nothing would be missed.

5. Comments were made about the heading of tables that included quality of life, but there was no quality of life data.
   Response: Quality of life was removed from the heading of the table.

6. Comments were made to increase the clarity of the document.
   Response: These changes were made in the document.

7. A comment was made about why was progression-free survival is longer in the EFGR + chemo group and OS is longer in the EGFR-only group in the Hirsh trial (60)?
   Response: We recognise it is an interesting observation, but there is no immediate answer.

8. A comment was made about how many patients crossed over in the five trials included in the meta-analysis of overall survival in EGFR inhibitors versus chemotherapy in molecularly selected patients.
   Response: the actual number is not given in the studies, but it is common knowledge that some patients did cross over.

9. A comment was made about the use of different schedules of erlotinib in two trials in table 3.
   Response: This has been changed in the document.

10. A comment was made concerning the difference between Time to Progression with erlotinib plus paclitaxel and carboplatin (12.5 months) compared to chemotherapy alone (6.6 months) p=0.092 (23). Even if this is not a statistically significant difference, is it a question of sample size?
    Response: This was an unplanned subanalysis, and this has now been changed in the document to provide better clarity.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Lung DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Lung DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review November 29, 2013)

Recommendation 1a
First-line therapy with an EGFR TKI is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients.

The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations.

Key Evidence
Twenty-five randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation (REFS). The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients.

Recommendation 1b
In patients with *EGFR* mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib, or afatinib is the preferred treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer progression-free survival and improved quality of life.

Qualifying Statement
There is no clear difference in overall survival. Many patients in these trials

randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative.

Key evidence
Six randomized trials and two meta-analyses comprised the evidence base. The trials and meta-analyses based on data from these trials showed that progression-free survival was prolonged in molecularly selected patients when an EGFR was used as first-line treatment.

- Five trials were included in the initial meta-analysis that showed an HR of 0.36 (95%CI, 0.27-0.48; p<0.00001).
- A second meta-analysis done on progression-free survival that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.39 (95%CI, 0.31-0.49; p<0.00001).
- All six trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy.

Recommendation 2
In patients well enough to consider second-line chemotherapy, an EGFR TKI can be recommended as second- or third-line therapy.

There is insufficient evidence to recommend the use of a second EGFR TKI, such as afatinib, in patients whose disease has progressed following chemotherapy and gefitinib or erlotinib, as available data does not demonstrate any improvement in overall survival

Qualifying Statements
There are data to support the use of an EGFR TKI in patients who have progressed on platinum-based chemotherapy. Erlotinib is known to improve overall survival and quality of life when used as second- or third-line therapy, in comparison to best supportive care.

However, available data would suggest that second-line therapy with either chemotherapy or an EGFR TKI results in similar progression-free and overall survival. Available evidence would support the use of either erlotinib or gefitinib in this situation.

Data from a randomized phase II trial suggests improved progression-free survival for dacomitinib versus erlotinib, but these data require confirmation in a phase III trial.

The Lux Lung 1 study failed to meet its primary outcome of improved overall survival. However, the study showed improved progression-free survival for patients randomized to afatinib and was associated with improvements in lung cancer symptoms.

Key Evidence

- Three studies examined an EGFR inhibitor as a second-line treatment against a placebo and best supportive care. One study reported on the use of erlotinib and showed a significant improvement in progression-free survival (p=0.001) and overall survival (p=0.001). The other two studies evaluated gefitinib, and

one study found significant results for response rate (p<0.0001), and the other for progression-free survival (p=0.002).

- A meta-analysis was done on five second-line studies and this showed no improvement with EGFR TKIs versus chemotherapy for progression-free survival (HR, 0.98; 95%CI 0.85-1.13, p=0.76) and overall survival (HR, 1.02; 95%CI, 0.94-1.11, p=0.64).
- One phase II study compared erlotinib to dacomitinib. This study showed significant results for dacomitinib for response rate (p=0.011) and for progression-free survival (p=0.012).
- The Lung Lux 1 study examined the use of afatinib in the third- and fourth-line setting against a placebo. This study showed improved PFS (HR, 0.38; 95%CI, 0.31-0.48, p<0.0001), but no difference in overall survival (HR, 1.08; 95%CI, 0.86-1.35, p=0.74).

Recommendation 3
An EGFR TKI is recommended as an option for maintenance therapy in patients who have not progressed after four cycles of a platinum-doublet chemotherapy. No recommendation can be made with respect to the choice of gefitinib or erlotinib.

Qualifying Statements

- Trials have evaluated both erlotinib and gefitinib. There are no trials directly comparing these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, but the overall survival advantage is modest for both agents.
- There are competing strategies of maintenance chemotherapy without an EGFR TKI, such as pemetrexed, that are not addressed in this guideline. The recommendation for TKI above should not be taken as excluding these other strategies as reasonable options; as this evidence was not reviewed, no statement can be made for or against these other strategies. The Lung DSG plans to develop a separate guideline on maintenance therapy as soon as possible.

Key evidence

Six studies evaluated the use of an EGFR inhibitor in the maintenance setting.

- Two of the trials reported a statistically significant survival benefit with erlotinib. One for response rate (p=0.0006) when compared to placebo and one for progression-free survival when combined with bevacizumab against bevacizumab (p=0.0012).
- One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs. 7%) and 9.1 months versus 8.3 months for overall survival.
- Two trials evaluating gefitinib found a statistically significant benefit for progression-free survival in the maintenance setting, p<0.001 when combined with chemotherapy and against chemotherapy and p<0.0001 compared to a placebo.
- Another trial evaluated gefitinib and showed a higher response rate, but this was not significant (p=0.369).

Toxicities
The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was

also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity.

Key evidence

- Two randomized phase II trials, each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients).
- One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib.
- One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs. 8%).

Methods

Targeted Peer Review: During the guideline development process, five targeted peer reviewers from Ontario, Quebec, Alberta and British Columbia considered clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on November 29, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Lung DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists in Ontario, who were in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey Web site where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on November 29, 2013. The consultation period ended on January 17, 2014. The Lung DSG reviewed the results of the survey.

Results

Targeted Peer Review: Five responses were received from five reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=5)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					5
2. Rate the guideline presentation.				1	4
3. Rate the guideline recommendations.			1		4
4. Rate the completeness of reporting.				4	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				3	2
6. Rate the overall quality of the guideline report.					
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					5
8. I would recommend this guideline for use in practice.					5

9. What are the barriers or enablers to the implementation of this guideline report?
Perhaps it would not conform to the structured layout of the guideline, but flow diagrams indicating where EGFR TKIs fit in the sequence of systemic therapy options for the various scenarios considered (i.e., unselected NSCLC patients, EGFR mutation-positive patients) might be a helpful visual aid. This could obviously include the specific EGFR TKIs recommended in the guideline at the different points in time.
Response:
This will most likely be tied into a disease pathway map.
Regulatory approval of certain agents in some provinces, i.e., Pemetrexed!
Availability of EGFR mutation testing.

Summary of Written Comments

The main points contained in the written comments were:

1. Several comments were made about minor typographical errors.
   Response: These have been addressed and corrected in the document.

2. Comment: In the Discussion, the repeated comments regarding crossover accounting for the lack of an overall survival benefit from first-line EGFR TKI in EGFR mutation positive patients need editing. The point about crossover can probably be made more succinctly.
   Response: This will be fixed in the document.

3. Should "Recommendation 2" include a statement regarding the second part of question 2, regarding a preferred sequence
   Response: Available data support the use of second line chemotherapy then third line EGFR TKI, or second line EGFR TKI then third line chemotherapy

4. Several comments were made about recent randomized trials not in the systematic review
   Response: The literature search will be updated and new studies added to the systematic review before it is published on the Web.

5. Comment: Very comprehensive. Covers all the areas where evidence exists. The only question I might raise is that the Recommendation 2 : Afatinib is not recommended as a second TKI because of lack of survival benefit. Recommendation 1 b does recommend a first line TKI for mutation positive patients despite lack of survival benefit. More explanation might be given for the difference.
   Response: The recommendation around afatinib is consistent with the data. The trial did not meet its primary outcome, and the drug did not receive a Health Canada indication as 3rd/4th line therapy
   The distinction between first line EGFR TKI trials and afatinib was that the first line trials were examining a question about sequence of therapy whereas the 3rd/4th line trial of afatinib was evaluating the addition of a new therapy

6. Comment: The impact of EGFRTKI's on EGFR negative patients is not clear. Evidence of benefit is getting weaker.
   Response: This comment is not supported by the data in the review. The Meta analysis of EGFR vs second line chemo shows no difference in overall survival, and BR21 supports the use of EGFR TKI after the failure of chemotherapy

7. Comment: They have done an excellent search of the literature and also analysis of the data. It should be pointed out that for this group of patients IPASS trial gives only sub analysis and that QOL was superior for Gefitinib, but LCS did not have a significant p-value. The afatinib trials LUX LUNG 3 and 6 support consistently the efficacy benefit of afatinib, they are the largest prospective trials, LUX LUNG 3 with the best comparator arm for non-squamous histology = Cis/Pem, which changes the HR as we see in Lux lung 3 vs. 6 and it is important to mention that there was an independent review for RR, which did not happen in i.e. IPASS trial.
   Response: The point being made here is that there may be some differences between trials. However, there are no direct comparisons between EGFR TKIs to allow any statement about the effectiveness of one EGFR TKI vs another. This is covered in the recommendations.

8. Comment: The compliance with the QOL questionnaires is important and also it is important which questionnaire it is, i.e. EURTAC Trial had poor compliance and only LCSS, QLQ LC 13,not C 30. Very frequently there is no mention of analgesic consumption when delay of pain is described. The LUX LUNG 3 and 6 have an excellent QOL analysis.
   Response: This is a reasonable point but does not influence our recommendations.

9. Comment: Some trials have other EGFR mutations, not only exon 19 deletion and exon 21 point mutation, i.e. LUX LUNG 3 trials. If you make comparisons you should look

also at the PFS of these patients. But I agree with the conclusion that for now we do not have a head to head comparison.
Response: Comments were added to the document.

Professional Consultation: Four responses were received. Key results of the feedback survey are summarized in Table 30.

Table 30. Responses to four items on the professional consultation survey.

	Number				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				*3*	*2*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				*1*	*4*
3. I would recommend this guideline for use in practice.				*1*	*4*

4. What are the barriers or enablers to the implementation of this guideline report?

1. Comment: Rapid access to EGFR testing will be an enabler. No EGFR or insufficient tissue will be a barrier. Cost and drug coverage could be barriers.

2. Comment: Required paperwork for coverage of these oral agents can be onerous. An online system to register patients would be a preferred route rather than generating forms / letters which require a manual res*ponse*.

Summary of Written Comments

1. Comment: I found at times that the report was confusing to read. I think it needs to qualify whether pts are mut neg or positive especially in the 2nd and 3rd line. At times it was hard to tell. If pts who are mut + and start with chemo for what ever reason then they should receive a TKI 2nd line absolutely. If pts are mut neg and have a good PS then they should not receive a TKI until 3rd line not in 2nd line. I do believe there is an option to reintroduce a TKI if pts are mut + later on in pts who had a TKI first line. I know there is no randomized data but that doesn't mean there is no data.
   Response: The comments about the sequence of second line TKI vs chemotherapy aren't really supported by the data in our review. Reintroduction of EGFR TKI has not been evaluated, and I don't think we can really provide a recommendation about this.

2. Comment: Needs to be coupled with a guideline looking at maintenance chemotherapy. Needs to comment on applicability of recommendations now that standard of care has evolved to include EGFR mutation status of all lung cancer

patients up front. Recommendation 3 needs to clarify for reader whether pertains to all comers or EGFR mutation patients only. Otherwise, a detailed succinct report.
Response: The Lung DSG is currently working on a maintenance therapy guideline. The document will be edited to address the other comments.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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