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REVIEW ARTICLE

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

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ABSTRACT

Introduction This systematic review addresses the use of epidermal growth factor receptor (EGFR) inhibitors in three populations of advanced non-small-cell lung cancer (NSCLC) patients—unselected, selected, and molecularly selected—in three treatment settings: first line, second line, and maintenance.

Methods Ninety-six randomized controlled trials found using the MEDLINE and EMBASE databases form the basis of this review.

Results In the first-line setting, data about the efficacy of EGFR tyrosine kinase inhibitors (TKIS) compared with platinum-based chemotherapy are inconsistent. Results from studies that selected patients based on clinical characteristics are also mixed. There is high-quality evidence that an EGFR TKI is preferred over a platinum doublet as initial therapy for patients with an activating mutation of the *EGFR* gene. The EGFR TKIS are associated with a higher likelihood of response, longer progression-free survival, and improved quality of life. Multiple trials of second-line therapy have compared an EGFR TKI with chemotherapy. Meta-analysis of those data demonstrates similar progression-free and overall survival. There is consequently no preferred sequence for second-line EGFR TKI or second-line chemotherapy. The EGFR TKIS have also been evaluated as switch-maintenance therapy. No molecular marker could identify patients in whom a survival benefit was not observed; however, the magnitude of the benefit was modest.

Conclusions Determination of *EGFR* mutation status is essential to making appropriate treatment decisions in patients with NSCLC. 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 the selected agent should be administered as second- or third-line therapy.

Key Words Non-small-small cell lung cancer, EGFR inhibitors, mutation status, systematic review

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INTRODUCTION

Lung cancer represents a major health burden. Many affected individuals present with advanced disease and are candidates for palliative systemic therapy. Historically, all patients with advanced non-small-cell lung cancer (NSCLC) would receive similar therapy, in which platinum doublets were recommended as initial (first-line) therapy[1,2], pemetrexed[3] or docetaxel[4,5] as second-line therapy, and erlotinib as second- or third-line therapy[6,7].

Significant changes have taken place in the approach to the treatment of advanced NSCLC since 2010. Treatment algorithms are now heavily influenced by the histologic subtype of NSCLC[8], and multiple trials have examined the sequence of subsequent lines of therapy [epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIS) vs. chemotherapy]. More importantly, the discovery of molecular abnormalities such as mutations of the *EGFR* gene[9,10] and translocations of the *ALK*[11] gene have identified a group of patients who appear to derive significantly greater benefit from molecularly targeted therapies.

METHODS

Four clinical members of the Program in Evidence-Based Care's Lung Cancer Disease Site Group and one

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methodologist selected and reviewed evidence related to EGFR TKIs in NSCLC. The body of evidence in this review primarily encompasses mature randomized controlled trial data.

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 (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx), the U.S. 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 conference proceedings from 2007 to 2013 were also searched. Search terms indicative of NSCLC, gefitinib (Iressa: AstraZeneca, Mississauga, ON), erlotinib (Tarceva: Genentech, San Francisco, CA, U.S.A.), afatinib, dacomitinib, and icotinib were used. Articles published before 2006 and included in this version of the systematic review were found using the search strategy described in the previous version of the guideline[6]. Only fully published articles from the previous version of this systematic review were included.

Study Selection Criteria

Publications were included in the review if they were meta-analyses or randomized trials (phase II or III) comparing gefitinib, erlotinib, afatinib, dacomitinib, or icotinib alone or in combination with chemotherapy with placebo, best supportive care, or chemotherapy; or comparing various doses or schedules of gefitinib, erlotinib, afatinib, dacomitinib, or icotinib; and 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.

Publications were excluded from the review if they were pilot trials, dose-escalation trials, or case series (including expanded access programs); letters and editorials that reported clinical trial outcomes; or 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. Because hazard ratios (HRS), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes[12], HRS 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.*[12]. A random effects model was used for all pooling.

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

RESULTS

Literature Search Results

Of the 3633 English and foreign-language studies identified, ninety-six randomized trials met the predefined eligibility criteria for the present systematic review. Of those trials, sixty-six were fully published reports, and thirty were in abstract form, including four updates to fully published trials. Slide presentations associated with abstract trial reports were also included if the presentations were publicly available on meeting Web sites and if they provided additional data. No relevant systematic reviews that answered our research questions were identified.

Outcomes

This report separately considers three populations of NSCLC patients (unselected, clinically selected, and molecularly selected). In the unselected group, any NSCLC patient was allowed to participate in the trial as long as the other trial eligibility criteria were met 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* mutation.

First-Line Treatment

Unselected Populations: *EGFR Inhibitor Compared with Chemotherapy:* Six fully published papers and three abstracts compared an EGFR inhibitor with platinum-based chemotherapy. Most of the trials were small, with fewer than 100 patients per arm. Only the TORCH trial appeared to have a sufficient number of participants to provide meaningful information on overall survival (OS)[13] (Table I). The findings of the trials suggest that first-line therapy with an EGFR TKI is inferior to chemotherapy in an unselected population of NSCLC patients.

Response rate was not reported in three studies. In one study, the response rate favoured the EGFR inhibitor[21], and in four studies, it favoured chemotherapy[13,14,19–21]. The study by Reck *et al.*[19] found a significantly higher response rate in patients randomized to chemotherapy ($p = 0.0001$).

The results show improved progression-free survival (PFS) for patients randomized to chemotherapy. Median PFS was similar in two trials[14,18]. In one trial, PFS was longer in the EGFR inhibitor group: 4.57 months for erlotinib versus 2.53 months for vinorelbine (HR: 0.6444; 95% CI: 0.4325 to 0.9601; $p = 0.0308$)[21]. In five trials, PFS was longer in the chemotherapy group[13,15,17,19,20]. Several of the trials found that PFS significantly favoured chemotherapy[13,15,19]. One trial examined time to progression and found that it was longer with chemotherapy, but not significantly so[20].

TABLE I First-line epidermal growth factor receptor (EGFR) inhibitors in unselected patients

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
First-line EGFR inhibitor compared with chemotherapy in unselected patients						
Crino *et al.*, 2008[14] (INVITE, phase II)	97 99		Gefitinib 250 mg daily Vinorelbine 30 mg/m^2	3.1% 5.1%	2.7 Months 2.9 Months HR: 1.19; 95% CI: 0.85 to 1.65 (p=0.310)	5.9 Months 8.0 Months HR: 0.98; 95% CI: 0.66 to 1.47 (p=0.272)
Lilenbaum *et al.*, 2008[15] (phase II)	52 51		Erlotinib 150 mg daily Carboplatin AUC 6 plus paclitaxel 200 mg/m^2	Not reported	1.91 Months 3.52 months HR: 1.45; 95% CI: 0.98 to 2.15 (p=0.063)	6.6 Months 95% CI: 3.78 to 8.25 months 9.5 Months 95% CI: 1.94 to 12.45 months
Kobayashi *et al.*, 2009[16] (phase III, abstract)	80 75		Gefitinib 250 mg daily Carboplatin AUC 6 plus paclitaxel 200 mg/m^2	Preliminary: 53.7% (both groups analyzed together)	6.5 Months	Not reported
Agarwal *et al.*, 2010[17] (phase II, abstract)	18 17		Gefitinib 250 mg daily Carboplatin AUC 5 plus gemcitabine 1000 mg/m^2	Not reported	42 Days 95% CI: 35 to 90 days 131 Days 95% CI: 63 to 268 days	138 Days 95% CI: 66 to 190 days 213 Days 95% CI: 101 to 399 days
Morere *et al.*, 2010[18] (IFCT-0301, phase II)	43 42 42	43 41 41	(A) Gefitinib 250 mg daily (B) Gemcitabine 1250 mg/m^2 (C) Docetaxel 75 mg/m^2	Not reported	1.9 Months 2.0 Months 2.0 Months (B VS. A: p=0.172) (C VS. A: p=0.078) (C VS. B: p=0.633)	2.2 Months 2.4 Months 3.5 Months (B VS. A: p=0.190) (C VS. A: p=0.088) (C VS. B: p=0.706)
Reck *et al.*, 2010[19] (phase II, abstract)	144 140		Erlotinib 150 mg daily 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 to 2.09 (p=0.0005)	7.3 Months 8.4 Months, HR: 1.24; 75% CI: 0.9 to 1.71
LeCaer *et al.*, 2011[20] (GFPC 0504, phase II)	51 48		Erlotinib 150 mg daily Docetaxel 30 mg/m^2 and gemcitabine 900 mg/m^2 Reverse on relapse	First-line: 17.6% Second-line: 11.8% First-line: 20.8% Second-line: 6.3%	TTP1: 2.7 months TTP2: 5.8 months TTP1: 4.7 months TTP2: 7.5 months (TTP1 and 2: p=0.53)	7.1 Months 9.4 Months

TABLE I Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
First-line EGFR inhibitor compared with chemotherapy in unselected patients						
Chen *et al.*, 2012[21] (phase II)	57		Erlotinib 150 mg daily	22.8%	4.57 Months	11.67 Months
	56		Vinorelbine 60 mg/m^2	8.9%	2.53 Months HR: 0.6444; 95% CI: 0.4325 to 0.9601 (p=0.0308)	9.3 Months (p=0.6975)
Gridelli *et al.*, 2012[13] (TORCH, phase III)	380		Erlotinib 150 mg daily	20.3%	6.4 Months	8.7 Months
	380		Cisplatin 80 mg/m^2 plus gemcitabine 1200 mg/m^2	32.6%	8.9 Months HR: 1.21; 95% CI: 1.04 to 1.42	11.6 Months HR: 1.22; 95% CI: 1.03 to 1.44
First-line EGFR inhibitor plus chemotherapy compared with chemotherapy alone in unselected patients						
Giaccone *et al.*, 2004[22] (INTACT 1, phase III)	365	365	Gefitinib 500 mg daily plus chemotherapy[a]	50.3% (166/330)	TTP: 5.5 months	9.9 Months/43%
	365	365	Gefitinib 250 mg daily plus chemotherapy[a]	51.2% (172/336)	TTP: 5.8 months	9.9 Months/41%
	363	363	Placebo plus chemotherapy[a]	47.2% (153/324)	TTP: 6.0 months (p=0.7633)	10.9 Months/44% (log rank p=0.456)
Herbst *et al.*, 2004[23] (INTACT 2, phase III)	347	347	Gefitinib 500 mg daily plus chemotherapy[b]	30.0%	4.6 Months	8.7 Months/37%
	345	345	Gefitinib 250 mg daily plus chemotherapy[b]	30.4%	5.3 Months	9.8 Months/41%
	345	345	Placebo plus chemotherapy[b]	28.7%	5.0 Months	9.9 Months/42% (at 1 year, p=0.6385)
Herbst *et al.*, 2005[24] (TRIBUTE, phase III)	539		Paclitaxel 200 mg/m^2 plus carboplatin AUC 6 plus erlotinib 150 mg daily	21.5%	Median TTP: 5.1 months	10.6 Months/46.9%
	540		Paclitaxel 200 mg/m^2 plus carboplatin AUC 6 plus placebo	19.3% (p=0.36)	Median TTP: 4.9 Months (p=0.36)	10.5 Months/43.8% HR: 0.995; 95% CI: 0.86 to 1.16 (p=0.95)
Gatzemeier *et al.*, 2007[25] (TALENT, phase III)	580		Erlotinib 150 mg daily plus chemotherapy[c]	31.5%	TTP: 23.7 weeks	43 Weeks 1-Year survival: 41%
	579		Placebo plus chemotherapy[c]	29.9%	TTP: 24.6 weeks HR: 0.98; 95% CI: 0.86 to 1.11 (p=0.74)	44.1 Weeks 1-Year survival: 42% HR: 1.06; 95% CI: 0.90 to 1.23 (p=0.49)

TABLE I Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
First-line EGFR inhibitor plus chemotherapy compared with chemotherapy alone in unselected patients						
Nokikara *et al.*, 2008[26] (phase II, abstract)	49		Carboplatin AUC 6 plus paclitaxel 200 mg/m^2 plus gefitinib 250 mg daily	Not reported	18.8 Months	1 Year/61.2%
	48		Gefitinib 250 mg daily until disease progression, followed by carboplatin AUC 6 plus paclitaxel 200 mg/m^2	Not reported	17.2 Months	1 Year/68.1%
Mok *et al.*, 2009[27] (phase II)	76		Erlotinib 150 mg daily plus gemcitabine 1250 mg/m^2 and either cisplatin 75 mg/m^2 or carboplatin AUC 5	35.5%	29.4 Weeks	74.1 Weeks
	78		Placebo plus gemcitabine 1250 mg/m^2 and either cisplatin 75 mg/m^2 or carboplatin AUC 5	24.4%	23.4 Weeks HR: 0.47; 95% CI: 0.33 to 0.6 (p=0.0002)	75.7 Weeks HR: 1.09; 95% CI: 0.70 to 1.69 (log rank p=0.42)
Riely *et al.*, 2009[28] (phase II)	28		Erlotinib 150 mg daily on days 1 and 2 followed by carboplatin AUC 6 plus paclitaxel 200 mg/m^2 on day 3	18% 95% CI: 6% to 37%	TTP: 4 months 95% CI: 3 to 5	10 Months 95% CI: 8 to 16 months 1-Year survival: 49% 2-Year survival: 25%
	29		Erlotinib 1500 mg daily on days 1 and 2 followed by carboplatin AUC 6 plus paclitaxel 200 mg/m^2 on day 3	34% 95% CI: 18% to 54%	TTP: 4 months 95% CI: 3 to 6	15 Months 95% CI: 8 months to NR 1-Year survival: 63% 2-Year survival: 42%
	29		Carboplatin AUC 6 plus paclitaxel 200 mg/m^2 on day 1 followed by erlotinib 1500 mg daily on days 2 and 3	28% 95% CI: 13% to 47%	TTP: 5 months 95% CI: 3 to 8	10 Months 95% CI: 5 to 16 months 1-Year survival: 48% 2-Year survival: 26%
Mok *et al.*, 2012[29] (FASTACT-II, phase III, abstract)	226		Chemotherapy[d] with inter-calculated erlotinib 150 mg daily, days 15–28	42.9%	7.6 Months	18.3 Months
	225		Chemotherapy[d] with placebo	17.8%	6 Months HR: 0.57; 95% CI: 0.46 to 0.70 (p<0.0001)	14.9 Months HR: 0.78; 95% CI: 0.60 to 1.02 (p=0.069)

TABLE I Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Other first-line trials in unselected patients						
Goss *et al.*, 2009[30] (phase II)	100		Gefitinib 250 mg daily plus BSC	6.0%	43 Days	3.7 Months
	101		Placebo plus BSC	1.0%	41 Days HR: 0.82; 95% CI: 0.60 to 1.12 (p=0.217)	2.8 Months HR: 0.84; 95% CI: 0.62 to 1.15 (p=0.272)
Gridelli *et al.*, 2011[31] (phase II)	29		Sorafenib 800 mg daily plus erlotinib 150 mg daily	10.3% 95% CI: 2.2% to 27.4%	TTP: 12.7 weeks 95% CI: 2.0 to 69.4 weeks	12.6 Months 51.9% (1-year) 95% CI: 36.0% to 74.8%
	31		Sorafenib 800 mg daily plus gemcitabine 1200 mg/m^2	6.5% 95% CI: 0.8% to 21.4%	TTP: 8.1 weeks 95% CI: 1.0 to 65.0 weeks	6.55 Months 35.2% (1-year) 95% CI: 21.4% to 57.7%
Stinchcombe *et al.*, 2011[32] (phase II)	44		Gemcitabine 1200 mg/m^2 (after disease progression, patients were offered erlotinib 150 mg daily)	7%	3.7 Months 95% CI: 2.3 to 4.7 months 6–22 Months 95% CI: 11 to 35 months	6.8 Months 95% CI: 4.8 to 8.5 months
	51		Erlotinib 150 mg daily	0%	2.8 Months 95% CI: 1.4 to 3.4 months 6–24 Months 95% CI: 13 to 36 months	5.8 Months 95% CI: 3.0 to 8.3 months 5.6 Months 95% CI: 3.5 to 8.4 months
	51		Erlotinib 100 mg daily plus gemcitabine 1000 mg/m^2	21%	1.1 Months 95% CI 2.4 to 5.0 months 6–25 Months 95% CI: 15 to 38 months	
Thomas *et al.*, 2011[33] (phase II, abstract)	111		Erlotinib 150 mg daily plus bevacizumab 15 mg/kg daily	12.6%	3.7 Months 95% CI: 2.8 to 4.3 months	12.6 Months 95% CI: 10.3 to 16.2 months
	113		Gemcitabine 1250 mg/m^2 and cisplatin 80 mg/m^2 plus bevacizumab 15 mg/kg daily	33.6%	7.2 Months 95% CI: 6.0 to 8.9 months	15.7 Months 95% CI: 11.9 to 21.7 months

TABLE I Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Other first-line trials in unselected patients						
Boutsikou *et al.*, 2013[34] (phase III)	61		Docetaxel 100 mg/m^2 plus carboplatin AUC 5.5	11%	TTP: 2.23 months	15.3 Months
	52		Docetaxel 100 mg/m^2 plus carboplatin AUC 5.5 plus erlotinib 150 mg daily	27%	TTP: 6.0 months	16.4 Months
	56		Bevacizumab 7.5 mg/kg plus docetaxel 100 mg/m^2 plus carboplatin AUC 5.5	23%	TTP: 6.0 months	19.1 Months
	60		Docetaxel 100 mg/m^2 plus carboplatin AUC 5.5 plus erlotinib 150 mg daily plus bevacizumab 7.5 mg/kg	20%	TTP: 7.3 months (Significant for combination: p=0.001)	22.1 Months (Did not differ between the four groups: p=0.381)
Lee *et al.*, 2014[35]	350		Erlotinib 150 mg daily plus BSC	Not reported	2.8 Months	3.7 Months
(TOPICAL, phase III)	320		Placebo plus BSC		2.6 Months	3.6 Months
					HR: 0.83;	HR: 0.94;
					95% CI: 0.71 to 0.97	95% CI: 0.81 to 1.10
					(p=0.019)	(p=0.46)

[a] Gemcitabine 1250 mg/m^2 plus cisplatin 80 mg/m^2.
[b] Paclitaxel 225 mg/m^2 plus carboplatin AUC 6.
[c] Gemcitabine 1250 mg/m^2 plus cisplatin 80 mg/m^2.
[d] Gemcitabine 1250 mg/m^2 plus carboplatin 5×AUC or cisplatin 75 mg/m^2.
CR = complete response; PR = partial response; HR = hazard ratio; CI = confidence interval; AUC = area under curve; TTP = time to progression.

One trial reported nonsignificant improvements in os in the EGFR inhibitor group[21]. In seven trials, os was prolonged with chemotherapy[13–15,17–20]. In the largest trial (TORCH), os was significantly worse for patients randomized to erlotinib[13]. Those findings suggest that initial therapy with an EGFR TKI in an unselected population of patients with advanced NSCLC could be inferior treatment.

Quality of life and symptom control were discussed in three trials[14,17,21]. In the trial by Crino *et al.*[14], the gefitinib group scored higher on all four of the quality of life assessment tools. The trials by Agarwal *et al.*[17] and Chen *et al.*[21] found no difference in quality of life, although the patients in the erlotinib group in the Chen *et al.* trial reported significantly better physical well-being.

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

EGFR Inhibitor Plus Chemotherapy Compared with Chemotherapy Alone: Eight trials examined the use of a first-line EGFR inhibitor plus chemotherapy compared with chemotherapy alone in unselected patients. Four trials evaluated continuous EGFR TKI plus chemotherapy, three trials evaluated intermittent EGFR TKI (intercalated), and one trial evaluated combination chemotherapy plus an EGFR TKI compared with sequential EGFR TKI followed by chemotherapy.

The data showed no benefit for the addition of an EGFR TKI to first-line chemotherapy, although the trial of intercalated EGFR TKI showed an improvement in PFS. No significant differences in the response rate were observed in four trials involving more than 4000 patients[22–25] (Table I). In three additional trials, the response rate favoured the EGFR inhibitor group[22–25,27–29]. In the trial by Riely *et al.*[28], the response rate was the highest (34%) for erlotinib 1500 mg daily, followed by paclitaxel and carboplatin chemotherapy. The response rate was 18% in the arm in which the dose of erlotinib was 150 mg, and 28% in the arm in which paclitaxel and carboplatin was followed by erlotinib 1500 mg daily.

Three trials reported PFS, with all reporting a longer PFS in the combined EGFR inhibitor and chemotherapy groups[23,27,29]. Statistical significance was reported in two of the trials, which both favoured the EGFR plus chemotherapy groups[27,29]. Four trials reported time to progression[22,24,25,28,34]. The INTACT 1 and 2, TRIBUTE, and TALENT trials all showed no significant difference in time to progression across all arms[22,24,25]. The trial by Riely *et al.*[28] did not show an increase in time to progression when erlotinib daily doses of 150 mg and 1500 mg were compared (both followed by paclitaxel and carboplatin): in both groups, time to progression was 4 months. The combination of paclitaxel and carboplatin followed by erlotinib 1500 mg daily showed a 1-month increase in time to progression. An unplanned subgroup analysis by mutation status for patients in the TRIBUTE trial with available tissue showed an increase in time to progression for erlotinib plus paclitaxel and carboplatin (12.5 months) compared with chemotherapy alone (6.6 months), but that difference did not reach significance ($p = 0.092$)[24].

There was no clear improvement in os with the addition of an EGFR TKI to chemotherapy. Statistical significance was not reached in any trial. In the trial by Riely *et al.*[28], survival was greatest with erlotinib 1500 mg daily followed by paclitaxel and carboplatin: 15 months compared with 10 months for both erlotinib 150 mg daily followed by paclitaxel and carboplatin, and paclitaxel and carboplatin followed by erlotinib 1500 mg daily. The FAST-ACT II trial observed a trend toward longer os favouring the chemotherapy plus erlotinib arm (HR: 0.78; 95% CI: 0.60 to 1.02; $p = 0.069$)[29]. Those results do not support the addition of an EGFR TKI to platinum-based chemotherapy. Toxicities were similar between the groups, with the exception of diarrhea and skin disorders, which occurred more frequently in the EGFR inhibitor groups.

Other First-Line Trials: Six additional trials evaluating various approaches of EGFR TKI and chemotherapy were identified; none showed evidence of improved os. In two trials evaluating an EGFR TKI compared with placebo in patients not suitable for chemotherapy, no clear differences in PFS or os were observed (Table I). Statistical significance was reached in the trial by Lee *et al.*[35] for PFS, but neither trial showed a difference in os[30,35]. Quality of life in the Goss *et al.*[30] trial was not different between the two arms. For gefitinib, the rates of improvement in quality of life were 21.1% [by the Functional Assessment of Cancer Therapy–Lung (FACT-L)], 15.8% (by the Trial Outcome Index), 32.9% (by the lung cancer subscale of the FACT-L), and 28.3% (by the Pulmonary Symptom Improvement test); for placebo, the corresponding rates were 20%, 13.8%, 30.89%, and 28.3% respectively.

In the 3-arm trial by Stinchcombe *et al.*[32], sequential and concurrent gemcitabine plus erlotinib both led to higher response rates and longer PFS than did erlotinib alone, although the differences were not statistically significant. The longest os was observed in patients receiving sequential chemotherapy followed by erlotinib. No clear difference in quality of life was evident using the Trial Outcome Index ($p = 0.76$), the lung cancer subscale of the FACT-L ($p = 0.85$), or the FACT-L ($p = 0.57$).

The two trials that compared an EGFR inhibitor plus a targeted agent with a targeted agent and chemotherapy showed mixed results[31,33]. The trial by Boutsikou *et al.*[34] used a factorial design to evaluate the addition of erlotinib and bevacizumab to cisplatin and docetaxel. No significant improvement in os was observed, although the response rate was highest in the chemotherapy plus erlotinib arm. Time to progression was significant and longest in the combination arm ($p = 0.001$).

Clinically Selected Populations: Three studies that compared an EGFR inhibitor with chemotherapy in clinically selected patients in the first-line setting (Table II) were identified. A large proportion of the patients in these trials crossed over to the alternative therapy at progression. The IPASS trial demonstrated significant improvements in response rate and PFS, but no difference in os[36]. No significant outcome differences were observed in the other two trials[38,39].

TABLE II First-line epidermal growth factor receptor (EGFR) inhibitors in clinically selected patients

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
First-line EGFR inhibitor compared with chemotherapy in clinically selected patients						
Mok *et al.*, 2009[36] (IPASS)	609		Gefitinib 250 mg daily	43%	5.7 Months, 24.9% (12-month)	18.8 Months
Yang *et al.*, 2010[37] (IPASS overall survival update, phase III, abstract)	608		Paclitaxel 200 mg/m^2 plus carboplatin AUC 5 or 6	32.2% OR: 1.59; 95% CI: 1.25 to 2.01 (p<0.001)	5.8 Months, 6.7% (12-month) HR: 0.74; 95% CI: 0.65 to 0.85 (p<0.001)	17.4 Months HR: 0.901; 95% CI: 0.793 to 1.023 (p=0.109)
Han *et al.*, 2012[38] (First-SIGNAL, phase III)	159 154		Gefitinib 250 mg daily Gemcitabine 1250 mg/m^2 plus cisplatin 75 mg/m^2	55.4% 46.0% HR: 1.198; 95% CI: 0.944 to 1.520 (p=0.138)	5.8 Months 6.4 Months HR: 0.932; 95% CI: 0.716 to 1.213 (p=0.604)	22.3 Months 22.9 Months
LeCaer *et al.*, 2012[39] (GFPC 0505, phase II)	50		Erlotinib 150 mg daily	First-line: 12% Second-line: 8%	TTP1: 2.2 months TTP2: 3.5 months	3.9 Months
	44		Gemcitabine 1250 mg/m^2 Reverse on relapse	First-line: 11.4% Second-line: 4.5%	TTP1: 2.5 months TTP2: 4.3 months (TTP1: p=0.58) (TTP2: p=0.55)	4.4 Months (p=0.26)
First-line EGFR inhibitor plus chemotherapy compared with an EGFR inhibitor in clinically selected patients						
Janne *et al.*, 2012[40] (CALGB 30406, phase II)	81		Erlotinib 150 mg daily	35%	5.0 Months 95% CI: 2.9 to 7.0 months	24.6 Months 95% CI: 18.4 to 33.8 months
	100		Erlotinib 150 mg daily plus paclitaxel 200 mg/m^2 plus carboplatin AUC 6	46%	6.6 Months 95% CI: 5.4 to 8.2 months (p=0.1988)	19.8 Months 95% CI: 14.4 to 27.8 months
First-line EGFR inhibitor plus chemotherapy compared with chemotherapy alone in clinically selected patients						
Choi *et al.*, 2013[41] (phase II, abstract)	44		Gefitinib 250 mg daily (days 2–15, 3-week cycle) plus paclitaxel 175 mg/m^2 plus carboplatin AUC 5	40.9%	4.13 Months	9.33 Months
	46		Paclitaxel 175 mg/m^2 plus carboplatin AUC 5	37.0%	4.13 Months HR: 0.941; 95% CI: 0.61 to 1.45 (p=0.781)	10.53 Months HR: 0.95; 95% CI: 0.58 to 1.54 (p=0.827)

TABLE II Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
First-line EGFR inhibitor compared with chemotherapy in clinically selected patients						
Michael *et al.*, 2012[42] (GATE, phase II, abstract)	26		Erlotinib 150 mg daily (days 15–28) plus gemcitabine 1000 mg/m^2	3.8%	10.3 Months	Not reported
	28		Gemcitabine 1000 mg/m^2	7.1%	8.0 Months HR: 1.3; 95% CI: 0.63 to 2.68 (p=0.4798)	
Liang *et al.*, 2010[43] (phase II, abstract)	25		Pemetrexed 500 mg/ m^2 plus cisplatin 75 mg/m^2 plus gefitinib 250 mg daily	Not reported	9.95 Months	74.8% (12-month) 59.6% (24-month)
	24		Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2		6.83 Months HR: 0.533; 95% CI: 0.272 to 1.044 (p=0.067)	93.3% (12-month) 71.1% (24-month)

CR = complete response; PR = partial response; AUC = area under curve; OR = odds ratio; CI = confidence interval; HR = hazard ratio.

Subgroup analyses for the IPASS and First-SIGNAL trials were done for patients with tumour samples available for *EGFR* mutation testing[36,38]. In the First-SIGNAL trial, *EGFR* mutation–positive patients treated with gefitinib (compared with those treated with 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 to 1.100; $p = 0.086$). The mutation-negative patients in the gemcitabine and cisplatin arm (compared with the those in the gefitinib arm) showed a trend toward a higher overall response rate (51.9% vs. 25.9%, $p = 0.051$) and longer PFS (HR: 1.419; 95% CI: 0.817 to 2.466; $p = 0.226$). The treatment arms showed no significant differences in OS according to *EGFR* mutation status (mutation-positive subgroup HR: 1.043; 95% CI: 0.498 to 2.182; mutation-negative subgroup HR: 1.000; 95% CI: 0.523 to 1.911; and mutation-unknown subgroup HR: 0.880; 95% CI: 0.639 to 1.210)[38].

Findings were similar in the IPASS trial: PFS was significantly longer for patients in the mutation-positive subgroup receiving gefitinib than for those receiving carboplatin–paclitaxel (HR: 0.48; 95% CI: 0.36 to 0.64; $p < 0.001$). In the mutation-negative subgroup, PFS was significantly shorter in patients receiving gefitinib than in those receiving carboplatin–paclitaxel (HR: 2.85; 95% CI: 2.05 to 3.98; $p < 0.001$). Results in the subgroup with unknown *EGFR* mutation status were similar to those for the overall population. The OS with gefitinib therapy trended longer in the mutation-positive subgroup (HR: 0.78; 95% CI: 0.50 to 1.20) than in the mutation-negative subgroup (HR: 1.38; 95% CI: 0.92 to 2.09) or in the mutation-unknown subgroup (HR: 0.86; 95% CI: 0.68 to 1.09)[36], which suggests that the benefit of first-line therapy with an EGFR TKI is limited to patients with tumours known to harbour an *EGFR* mutation. Clinical characteristics should not be used to select patients for first-line EGFR TKI therapy.

One trial evaluated the combination of an EGFR TKI plus chemotherapy compared with an EGFR TKI alone in clinically selected patients. The response rate was greater in the EGFR inhibitor plus chemotherapy arm; however, no significant differences in PFS ($p = 0.1988$) or OS[40] were observed. Adverse effects were consistent with those associated with chemotherapy and EGFR inhibitors[40].

Three additional trials compared the combination of an EGFR TKI plus chemotherapy with chemotherapy alone in clinically selected patients. The addition of gefitinib to cisplatin and pemetrexed resulted in a trend toward longer PFS, but no improvement in OS[43]. No clear benefit was observed in the other two trials evaluating the addition of gefitinib to carboplatin and paclitaxel[41] or of erlotinib to gemcitabine[42].

Results for symptom control and quality of life were addressed in two studies. In the IPASS trial, statistical and clinically relevant improvements in quality of life were associated with the use of the EGFR inhibitor[36]. The First-SIGNAL trial found significant differences in physical ($p < 0.001$) and social functioning ($p = 0.013$) favouring gefitinib. No significant differences in emotional and cognitive functioning were observed[38].

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

Molecularly Selected Populations: Seven trials used an EGFR inhibitor in molecularly selected patients with stage IIIB/IV NSCLC. One trial selected patients on the basis of EGFR protein overexpression (assessed by immunohistochemistry) or increased gene copy number (assessed by fluorescence *in situ* hybridization, Table III). Six trials selected patients with tumours harbouring an *EGFR* mutation. A meta-analysis of this group of patients was performed because the patients were homogenous, and the treatment comparators were platinum-based chemotherapy regimens. All six trials observed higher response rates favouring the EGFR inhibitor group. Three of the trials (Mitsudomi *et al.*[46], Zhou *et al.*[48] and Yang *et al.*[51]) found the results to be statistically significant ($p < 0.0001$).

In every trial, PFS was also statistically significant and favoured the EGFR inhibitor[44,46,48,50–52]. A meta-analysis [Figure 1(A)] demonstrated a statistically significant improvement in PFS (HR: 0.35; 95% CI: 0.28 to 0.45; $p < 0.00001$). However, the I^2 is high at 80%, which shows considerable statistical heterogeneity. In each of the subgroup analyses (different EGFR inhibitors), the I^2 also remains high. The cause of the heterogeneity remains unknown at this time.

The addition of the subgroup analyses from both the IPASS and First-SIGNAL trials in patients with a known *EGFR* mutation status[36,38] resulted in similar findings [HR: 0.38; 95% CI: 0.31 to 0.46; $p < 0.00001$; Figure 1(B)]. Evidence of statistical heterogeneity remains, with an I^2 of 76%.

Six trials reported OS. The data are difficult to interpret, because many patients are likely to have crossed over to the other treatment arm, but the actual percentages are not reported. Meta-analysis of those trials demonstrates no difference in survival between the two groups [HR: 1.01; 95% CI: 0.86 to 1.18; $p = 0.94$; Figure 2(A)]. Inclusion of data from the IPASS and First-SIGNAL trials did not change that result [HR: 0.98; 95% CI: 0.84 to 1.14; $p = 0.77$; Figure 2(B)].

One additional study compared an EGFR inhibitor plus chemotherapy with an EGFR inhibitor alone in patients with EGFR protein overexpression or increased gene copy number[53]. No clear recommendation can be made from that trial. Response rate and PFS were higher in the EGFR plus chemotherapy group, but OS favoured the EGFR-inhibitor-alone group The most significant toxicity was skin rash, which occurred in slightly higher numbers in the EGFR-inhibitor-alone group[53].

Symptom control and quality of life were discussed in the Yang *et al.*[51] and Wu *et al.*[52] studies. A significant delay in time to deterioration of the 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[51]. A higher proportion of patients in the afatinib group experienced a significantly longer time to deterioration (HR: 0.56; 95% CI: 0.41 to 0.77; $p = 0.0002$)[52].

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

Second-Line Treatment

Unselected Populations: *EGFR Inhibitor Compared with Chemotherapy:* Ten studies[54–63] compared an EGFR inhibitor with chemotherapy (docetaxel or pemetrexed) in second-line treatment (Table IV). None of the trials incorporated a planned crossover to the other agent at the time of progression. However, at progression, patients were permitted to receive the alternative treatment to which they were assigned. No significant difference in response rate was observed in six of the ten studies[54,55,57,59–61,63]. In three of the four studies conducted in Asian populations, the EGFR inhibitor was associated with a significantly higher response rate[56,58,63].

The foregoing trials underwent meta-analysis for PFS and OS because they addressed similar questions and included clinically homogenous populations [Figure 3(A,B)]. (Three of the studies did not provide enough data to be included in the analysis[54,57,59].) No difference in PFS was observed between EGFR TKI and chemotherapy (HR: 0.99; 95% CI: 0.87 to 1.312; $p = 0.83$). The I^2 in this analysis was 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, and mutation status, and *KRAS* mutation status were not predictive of any difference in OS for either gefitinib or docetaxel[68]. For patients treated with gefitinib, *EGFR* mutation status predicted a longer PFS (HR: 0.16; 95% CI: 0.05 to 0.49; $p = 0.001$). However, the overall results suggest that second-line therapy with an EGFR TKI or with chemotherapy are both reasonable alternatives.

Similar results were observed for OS. A meta-analysis showed no difference in OS for second-line EGFR TKI or chemotherapy [HR: 1.02; 95% CI: 0.95 to 1.09; $p = 0.56$; Figure 3(B)]. There did not appear to be significant heterogeneity between the trials for OS (I^2: 0%).

Four studies evaluated symptom control and quality of life. All four found that the use of an EGFR inhibitor improved both symptom control and quality of life[54,56,58,60]. Adverse effects were consistent with those associated with EGFR inhibitors and chemotherapy.

EGFR Inhibitor Alone Compared with EGFR Inhibitor Plus Chemotherapy: Five studies compared an EGFR inhibitor alone with an EGFR inhibitor (concurrent or intercalated) plus chemotherapy. Three of those trials had small patient numbers[64–66].

The response rate showed no clear improvement with an EGFR TKI combined with another agent than with an EGFR TKI alone (Table IV). In several trials, small improvements in PFS were noted in favour of the combination arm, but no statistically significant differences were observed[64–67,69]. Overall survival followed a similar pattern. All but one of the studies[65] showed that OS was longer with an EGFR inhibitor plus another agent; in one study, the difference was statistically significant[69]. However, these reports come from small, inadequately powered trials, and so it is not possible to draw any real conclusions from the data.

Symptom control and quality of life were evaluated in the two studies by Chen and colleagues[64,66]. Using the Lung Cancer Symptom Scale, both studies found no difference in symptoms between the two groups. Adverse effects were consistent with those known for EGFR inhibitors and chemotherapy.

TABLE III First-line epidermal growth factor receptor (EGFR) inhibitor in molecularly selected patients

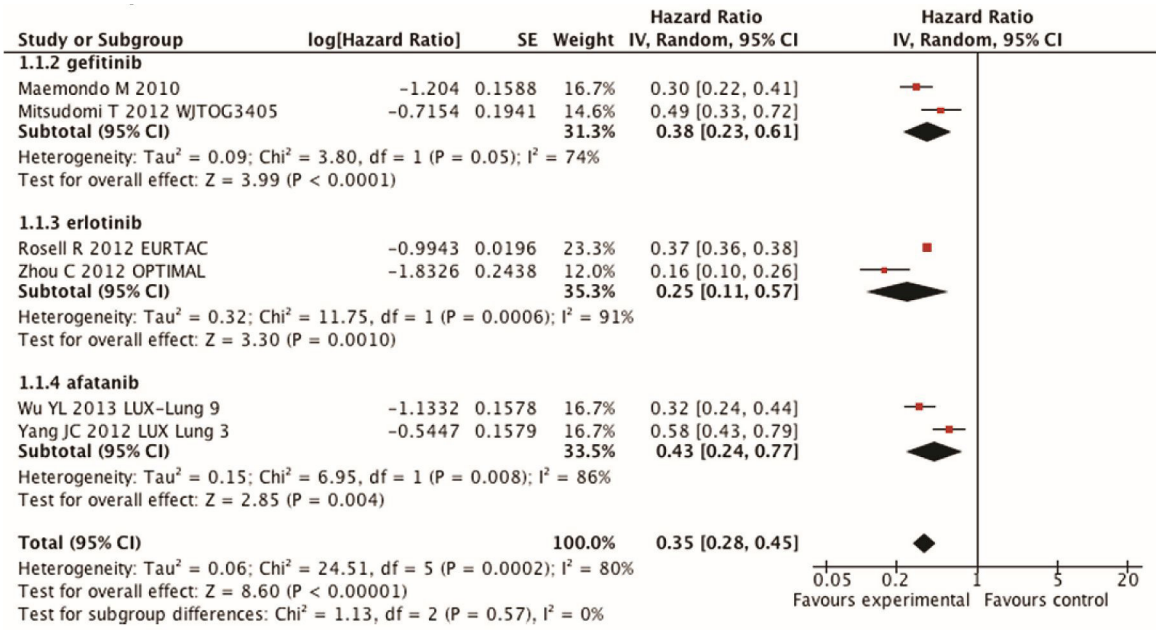
Reference (study details)	Patients (*n*) Enrolled	Analyzed	Treatment	Response rate (CR+PR)	Median survival Progression-free	Overall
EGFR inhibitor plus chemotherapy compared with EGFR inhibitor in patients with tumours harbouring an egfr mutation						
Maemondo *et al.*, 2010[44], and Inoue *et al.*, 2011[45] (NEJ002 and NEJ002 update, phase III, abstract)	115		Gefitinib 250 mg daily	73.7%	10.8 Months 42.1% (1-year) and 8.4% (2-year)	27.7 Months 57.9% (2-year)
	115		Paclitaxel 200 mg/m^2 plus carboplatin AUC 6	30.7% (p<0.001)	5.4 Months 3.2% (1-year) and 0% (2-year) HR: 0.30; 95% CI: 0.22 to 0.41 (p<0.001)	26.6 Months 53.7% (2-year) HR: 0.887; 95% CI: 0.634 to 1.241 (p=0.483)
Mitsudomi *et al.*, 2010[46,47] (WJTOG 3405, phase III)	86		Gefitinib 250 mg daily	62.1%	9.2 Months 95% CI: 8.0 to 13.9 months	36 Months
	86		Docetaxel 60 mg/m^2 plus cisplatin 80 mg/m^2	32.2% 95% CI: 12.6% to 74.1% (p<0.0001)	6.3 Months 95% CI: 5.8 to 7.8 months In favour of gefitinib: HR: 0.489; 95% CI: 0.336 to 0.710 (p<0.0001)	39 Months HR: 1.185; 95% CI: 0.767 to 1.829
Zhou *et al.*, 2011[48,49] (OPTIMAL, CTONG-0802, phase III)	83		Erlotinib 150 mg daily	83%	13.1 Months 95% CI: 10.58 to 16.53 months	Did not differ significantly between treatment arms: HR: 1.065 (p=0.6849)
	82		Gemcitabine 1000 mg/m^2 plus carboplatin AUC 5	36% (p<0.0001)	4.6 Months 95% CI: 4.21 to 5.42 months HR: 0.16; 95% CI: 0.10 to 0.26 (p<0.0001)	
Rosell *et al.*, 2012[50] (EURTAC, phase III)	86		Erlotinib 150 mg daily	54.6%	9.7 Months	19.3 Months
	87		Cisplatin 75 mg/m^2 plus 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	14.9%	5.2 Months HR: 0.37; 95% CI: 0.25 to 0.54 (p<0.0001)	19.5 Months HR 1.04; 95% CI: 0.65 to 1.68 (p=0.870)

TABLE III Continued

Reference (study details)	Patients (*n*) Enrolled	Analyzed	Treatment	Response rate (CR+PR)	Median survival Progression-free	Overall
EGFR inhibitor plus chemotherapy compared with EGFR inhibitor in patients with tumours harbouring an EGFR *mutation*						
Yang *et al.*, 2012[51] (LUX-Lung 3, phase III, abstract)	230		Afatinib 40 mg daily	56%	11.1 Months	
	115		Pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2	23% (p<0.0001)	6.9 Months HR: 0.58; 95% CI: 0.43 to 0.78 (p=0.0004)	
Wu *et al.*, 2013[52] (LUX-Lung 6, phase III)	242		Afatinib 40 mg daily	66.9%	11 Months	22.1 Months
	122		Gemcitabine 1000 mg/m^2 plus cisplatin 75 mg/m^2	23.0%	5.6 Months HR: 0.28; 95% CI: 0.20 to 0.39	22.2 Months HR: 0.95; 95% CI: 0.68 to 1.33 (p=0.76)
EGFR inhibitor plus chemotherapy compared with EGFR inhibitor alone in patients with EGFR protein overexpression or increased gene copy number						
Hirsch *et al.*, 2011[53] (phase II)	72	69	Erlotinib 150 mg daily	11.6%	2.69 Months 30.7% (6-month)	16.7 Months 59% (1-year)
	71	68	Erlotinib 150 mg daily plus paclitaxel 200 mg/m^2 plus carboplatin AUC 6	22.4%	4.57 Months 26.4% (6-month)	11.43 Months 46% (1-year)

CR = complete response; PR = partial response; AUC = area under curve; HR = hazard ratio; CI = confidence interval.

(A)



(B)

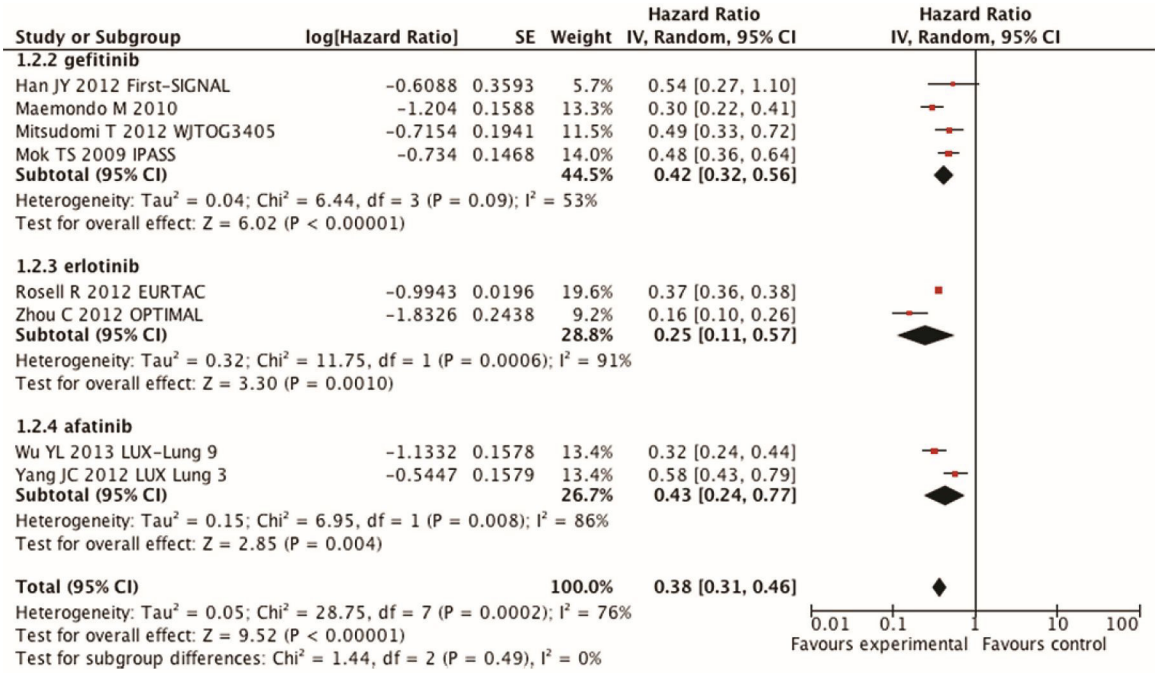
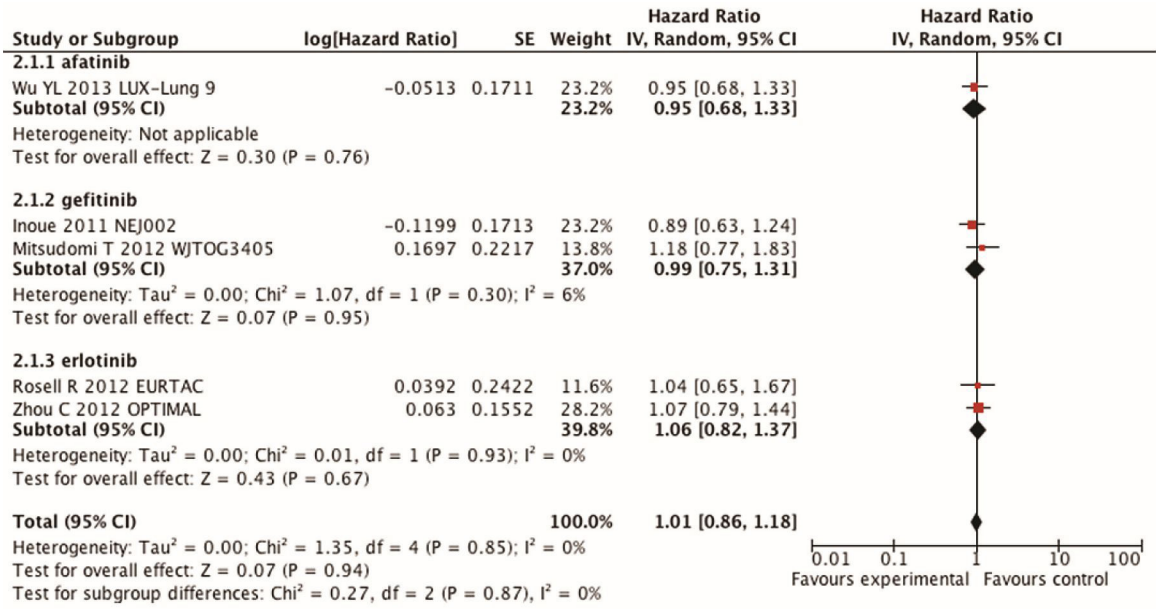


FIGURE 1 (A) Meta-analysis of progression-free survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected patients. (B) Meta-analysis of progression-free survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected patients, including those in the IPASS and First-SIGNAL trials. SE = standard error; IV = inverse variance; CI = confidence interval.

EGFR Inhibitor Alone or in Combination with a Targeted Agent: Seventeen studies examined an EGFR inhibitor alone or in combination with a targeted agent. This group of trials is heterogeneous. Many are small randomized phase II trials (Table V). Twelve studies evaluated an EGFR inhibitor alone compared with an EGFR inhibitor plus another targeted agent[71,73–75,78,79,81–86], and five additional studies examined various combinations of EGFR inhibitors and targeted agents[70,72,76,77,80].

No clear trend in response rate was evident. Some results favoured the EGFR inhibitor alone[71,79], some favoured the combination arm[70,78,82–86], and some found no difference between groups[76,77]. Progression-free survival followed the same trend as response rate. A number of trials

(A)



(B)

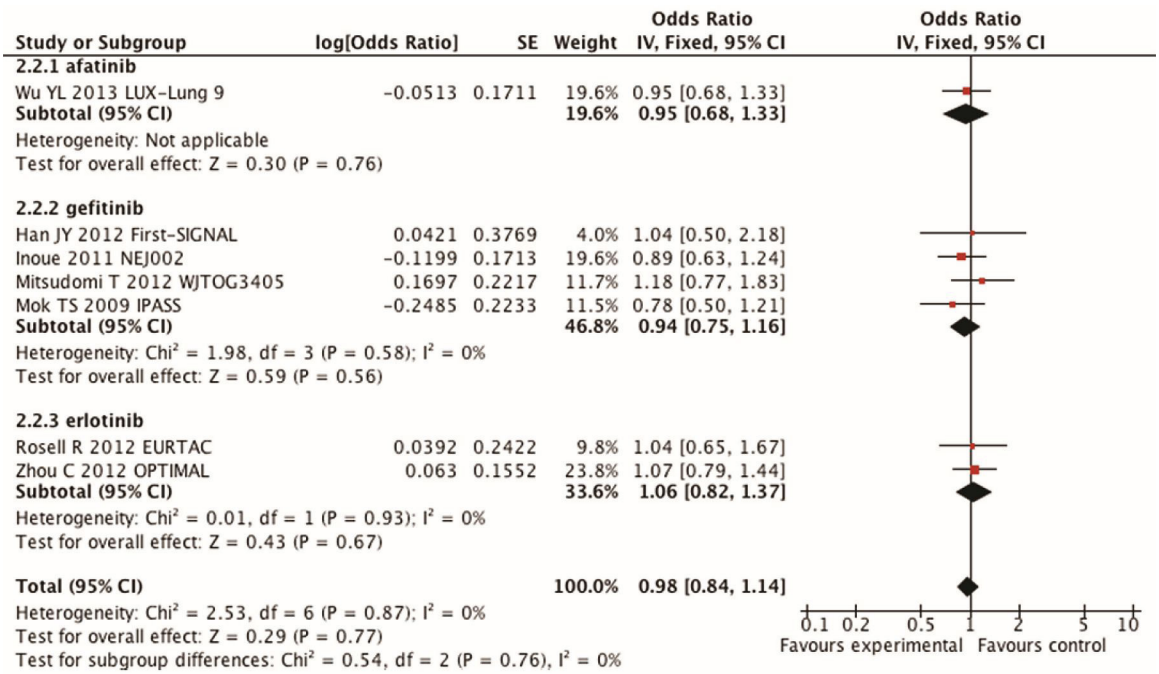


FIGURE 2 (A) Meta-analysis of overall survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected patients. (B) Meta-analysis of overall survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected patients, including those in the IPASS and First-SIGNAL trials. SE = standard error; IV = inverse variance; CI = confidence interval.

demonstrated improved PFS for the combination of an EGFR inhibitor and a targeted agent. However, none of the trials demonstrated any statistically significant improvements in OS[74]. Despite the heterogeneous nature of the trials, it is reasonable to conclude that no available evidence currently supports the combination of erlotinib with another targeted agent.

Symptom control and quality of life were reported in two studies. The study by Scagliotti *et al.*[82] also found no statistical difference in the mean health index score on the EQ-5D (EuroQoL, Rotterdam, Netherlands) between treatment groups ($p = 0.3373$). The study by Natale *et al.*[76] found that scores on the European Organisation for Research and Treatment of Cancer's 30-question Quality of Life

TABLE IV Second-line epidermal growth factor receptor (EGFR) inhibitor in unselected patients

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with chemotherapy in unselected patients						
Cufer 2 *et al.*, 2006[54] (SIGN, phase II)	68		Gefitinib 250 mg daily	13.2%	3.0 Months 65.6% (6-month)	7.5 Months
	73		Docetaxel 75 mg/m^2	13.7%	3.4 Months 56.1% (6-month)	7.1 Months
Kim *et al.*, 2008[55] (INTEREST, phase III)	733		Gefitinib 250 mg daily	27.2%	2.2 Months 19% (6-month)	7.6 Months 32% (1-year)
	733		Docetaxel 75 mg/m^2	31.1%	2.7 Months 18% (6-month) HR: 1.04; 95% CI: 0.93 to 1.18	8.0 Months 34% (1-year) HR 1.020; 95% CI: 0.905 to 1.150
Maruyama *et al.*, 2008[56] (V-15–32, phase III)	245	244	Gefitinib 250 mg daily	22.5%	2 Months (both groups)	11.5 Months and 47.8% (1-year)
	244	239	Docetaxel 60 mg/m^2	12.8% OR: 2.14; 95% CI: 1.21 to 3.78 (p=0.009)	HR: 0.90; 95% CI: 0.72 to 1.12 (p=0.335)	14.0 Months and 53.7% (1-year) HR: 1.12; 95% CI: 0.89 to 1.40 (p=0.330)
Hong *et al.*, 2010[57] (phase II, abstract)	32		Pemetrexed 500 mg/m^2	6.3%	2.0 Months	8.1 Months
	34		Gefitinib 250 mg daily	11.8% (p=0.74)	2.3 Months (p=0.74)	7.9 Months (p=0.60)
Lee *et al.*, 2010[58] (ISTANA, phase III)	82		Gefitinib 250 mg daily	28.1%	3.3 Months 32% (6-month)	14.1 Months
	79		Docetaxel 75 mg/m^2	7.6% (p=0.0007)	3.4 Months 13% (6-month) HR: 0.729; 90% CI: 0.533 to 0.998 (1-sided p=0.0441)	12.2 Months HR 0.870; 95% CI: 0.613 to 1.236 (2-sided p=0.4370)
Vamvakas *et al.*, 2010 (phase III, abstract)[59]	147		Pemetrexed 500 mg/m^2	11.6%	TTP: 2.9 months	8.9 Months
	150		Erlotinib 150 mg daily	6.8% (p=0.166)	TTP: 3.6 months (p=0.434)	7.7 Months (p=0.528)

TABLE IV Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with chemotherapy in unselected patients						
Ciuleanu *et al.*, 2012[60] (TITAN, phase III)	203		Erlotinib 150 mg daily	7.9%	6.3 Weeks	5.3 Months
	221		Docetaxel or pemetrexed, dose determined by centre	6.3%	8.6 Weeks HR: 1.19; 95% CI: 0.97 to 1.46 (p=0.089)	5.5 Months HR: 0.96; 95% CI: 0.78 to 1.19 (p=0.73)
Karampeazis *et al.*, 2013[61] (phase III)	179		Erlotinib 150 mg daily	9.0%	3.6 Months	8.2 Months
	178		Pemetrexed 500 mg/m^2	11.4% (p=0.469)	2.9 Months (p=0.136)	10.1 Months (p=0.986)
Okano *et al.*, 2013[62] (DELTA, phase III, abstract)	150		Erlotinib 150 mg daily	Not reported	2.0 Months	14.8 Months
	151		Docetaxel 60 mg/m^2		3.2 Months HR: 1.22; 95% CI: 0.97 to 1.55 (p=0.092)	12.2 Months HR: 0.91; 95% CI: 0.68 to 1.22 (p=0.527)
Kelly *et al.*, 2012[63] (phase II)	101		Erlotinib 150 mg daily	7%	2.8 Months	7 Months
	100		Pralatrexate 190 mg/m^2	2%	3.4 Months HR 0.91; 95% CI: 0.63 to 1.32	6.7 Months HR: 0.84; 95% CI: 0.61 to 1.14
Second-line EGFR inhibitor compared with EGFR inhibitor plus chemotherapy in unselected patients						
Chen *et al.*, 2007[64] (phase II)	27		Gefitinib 250 mg daily	55.6% (15/27)	TTP: 7.1 months	13.3 Months 51.3% (1-year)
	21		Vinorelbine 15 mg/m^2 plus gefitinib 250 mg daily	52.4% (11/21) (p=0.837)	TTP: 12.8 months (p=0.1331)	23.4 Months (p=0.1231) 75.3% (1-year) (p=0.133)
Aparisi *et al.*, 2011[65] (phase II, abstract)	34		Docetaxel 75 mg/m^2 plus intermittent erlotinib 150 mg daily	Not reported	2.3 Months 95% CI: 1.9 to 3.1	4.9 Months 95% CI: 2.7 to [*sic*]
	36		Erlotinib 150 mg daily		3.1 Months 95% CI: 2.0 to 4.5	6.0 Months 95% CI: 2.5 to 6.0

TABLE IV Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with EGFR inhibitor plus chemotherapy in unselected patients						
Chen *et al.*, 2011[66] (phase II)	58		Gefitinib 250 mg daily	35%	5.3 Months 18% (1-year)	18.3 Months 64.8% (1-year) 27.7% (2-year)
	57		Oral tegafur–uracil 1 capsule daily plus gefitinib 250 mg daily	37% (p=0.847)	8.3 Months 36.7% (1-year) HR: 0.65; 95% CI: 0.43 to 0.97	23.6 Months 68.1% (1-year) 47.1% (2-year)
Aerts *et al.*, 2013[67] (NVALT-10, phase II)	115		Erlotinib 150 mg daily	Not reported	4.9 Months	5.5 Months
	116		Erlotinib 150 mg daily on days 2–16 every 21 days, plus docetaxel 75 mg/m^2 for squamous disease or pemetrexed 500 mg/m^2 for nonsquamous disease		6.1 Months HR: 0.76; 95% CI: 0.58 to 1.02 (p=0.06)	7.8 Months HR: 0.67; 95% CI: 0.49 to 0.91 (p=0.01)

CR = complete response; PR = partial response; HR = hazard ratio; CI = confidence interval; OR = odds ratio; TTP = time to progression.

Questionnaire was similar between the groups: erlotinib 80% and vandetanib 82%. Adverse effects were in line with those commonly associated with EGFR inhibitors and chemotherapy.

EGFR Inhibitor Plus Chemotherapy Compared with Chemotherapy Alone: One study of 165 patients examined the use of an EGFR inhibitor plus chemotherapy compared with chemotherapy alone (Table VI). That study demonstrated a greater response rate and longer PFS for chemotherapy plus an EGFR inhibitor. The result for PFS was significant (HR: 0.63; 95% CI: 0.44 to 0.90; $p = 0.005$). In addition, OS was prolonged in the combination arm, and that result was significant (HR: 0.68; 95% CI: 0.47 to 0.98; $p = 0.019$)[87]. Given the small size of the trial, the evidence is insufficient to recommend the combination of an EGFR TKI plus chemotherapy.

EGFR Inhibitor Compared with Placebo: Three fully published studies compared an EGFR inhibitor with placebo[7,88,89]. The trial by Shepherd *et al.* (NCIC BR.21, examining erlotinib versus placebo) and the ISEL trial of gefitinib compared with placebo both showed response rates significantly better with the EGFR inhibitor than with placebo[7,88]. Significant improvements in PFS were also observed in both trials, as well as in the third trial of gefitinib versus placebo[89]. However, only the BR.21 trial of erlotinib demonstrated a significant improvement in OS. Erlotinib is recommended as second- or third-line therapy in patients who are not candidates for further chemotherapy.

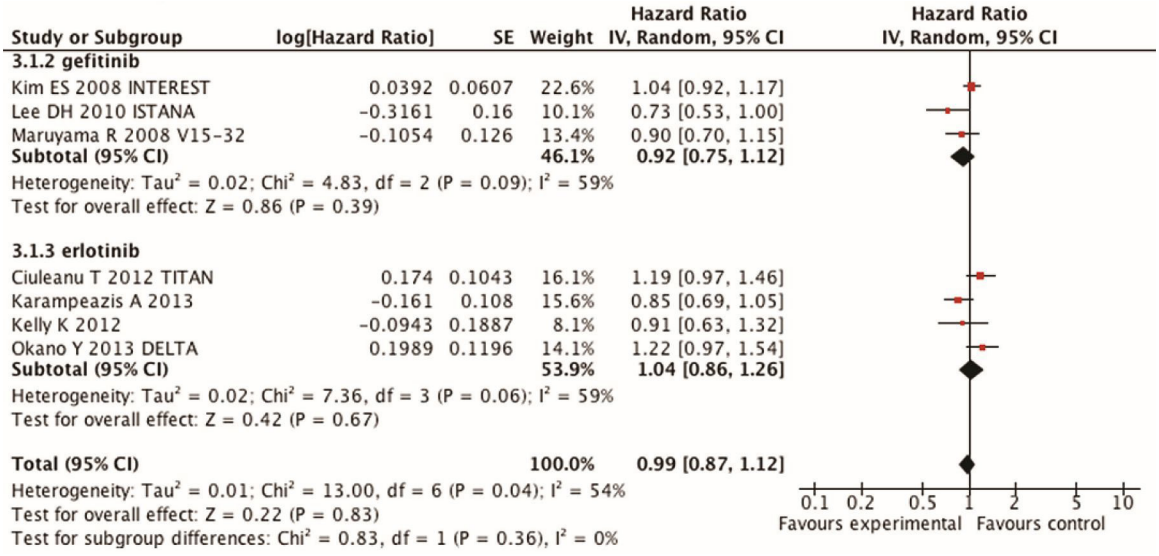
Correlative studies from BR.21, reported by Tsao *et al.*[90], evaluated the association between OS and *EGFR* mutation status, EGFR protein expression, and *EGFR* gene copy number. Survival was longer in the erlotinib group than in the placebo group when EGFR protein was overexpressed (HR: 0.68; 95% CI: 0.49 to 0.95; $p = 0.02$).

Symptom control and quality of life were addressed in two studies[7,88]. Time to deterioration of symptoms of cough ($p = 0.04$), dyspnea ($p = 0.03$), and pain ($p = 0.04$) was prolonged and significant with erlotinib in the study by Shepherd *et al.*[7]. Symptom improvement was significant with gefitinib in the study by Thatcher *et al.*[88] ($p = 0.019$). Adverse effects were also in line with those associated with use of EGFR inhibitor.

EGFR Inhibitor Compared with EGFR Inhibitor: Five studies compared EGFR inhibitors or dosing of the same EGFR inhibitor. The IDEAL 1 and 2 trials compared two dose levels of gefitinib and found no difference in any of the reported outcomes (Table VI). Similarly, the ICOGEN trial comparing gefitinib with icotinib and a second trial comparing gefitinib with erlotinib reported no difference in outcomes. A randomized phase II trial comparing dacomitinib with erlotinib demonstrated a significant improvement in response rate and PFS favouring dacomitinib and a trend toward improvement in OS[94]. However, those findings require confirmation in a phase III trial.

Quality of life was addressed in the two IDEAL studies. No differences in symptom response were evident for the different doses of gefitinib[91,92]. Adverse effects were consistent

(A)



(B)

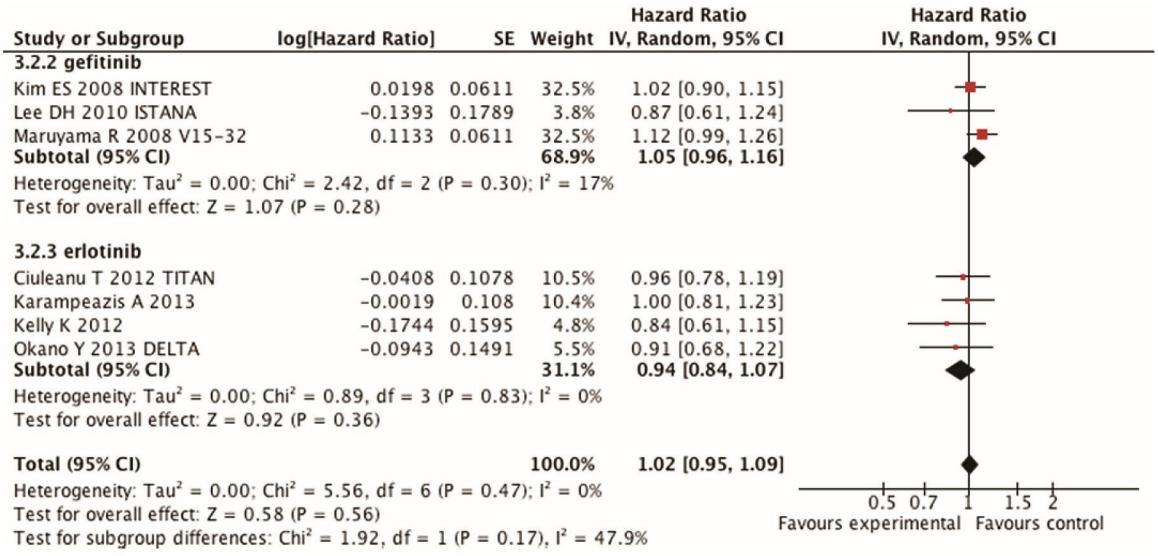


FIGURE 3 (A) Meta-analysis of progression-free survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in second-line unselected patients. (B) Meta-analysis of overall survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in second-line unselected patients. SE = standard error; IV = inverse variance; CI = confidence interval.

with those known for EGFR inhibitors. The adverse effects were slightly elevated with gefitinib 500 mg daily.

Clinically Selected Populations: *EGFR Inhibitor Compared with Chemotherapy:* Two trials compared pemetrexed with an EGFR inhibitor as second-line therapy in never-smokers (Table VII). The overall response rate was significantly higher for gefitinib (30.1% vs. 14.9%, $p < 0.001$)[96]. Progression-free survival 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 vs. 3.8 months for erlotinib and 4.4 months for pemetrexed alone; HR: 0.57; 95% CI: 0.40 to 0.81; $p = 0.002$)[97]. However, the survival rates were nonsignificantly different ($p = 0.89$)[96,97].

One study examined the use of gefitinib in patients with nonsquamous disease in the second-line setting (Table VII)[98]. No difference in the response rate was observed; however, PFS was significantly better with pemetrexed (4.8 months vs. 1.6 months with gefitinib; HR: 0.51; 95% CI: 0.36 to 0.73; $p < 0.001$)[98]. Overall survival was not yet reached for this trial.

Third- or Fourth-Line EGFR Inhibitor Compared with Placebo: The LUX-Lung 1 trial evaluated afatinib in patients who had received 1 or 2 prior chemotherapy treatments

TABLE V Second-line epidermal growth factor receptor (EGFR) inhibitor alone or in combination with a targeted agent in unselected patients

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Herbst *et al.*, 2007[70] (phase II)	39		Bevacizumab 15 mg/kg plus erlotinib 150 mg daily	17.9%	4.4 Months	13.7 Months 57.4% (1-year)
	40		Bevacizumab 15 mg/kg plus docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2	12.5%	4.8 Months	12.6 Months 53.8% (1-year)
	41		Docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 plus placebo	12.2%	3.0 Months	8.6 Months 33.1% (1-year)
Lynch *et al.*, 2009[71] (phase II)	25	25	Erlotinib 150 mg daily	4 (16%)	TTP: 2.7 months PFS: 2.7 months	7.3 Months 40% (1-year)
	25	22	Erlotinib 150 mg daily plus bortezomib 1.6 mg/m^2	2 (9%)	TTP: 1.5 months PFS: 1.3 months	8.5 Months 30% (1-year)
Natale *et al.*, 2009[72] (phase II)	85 83		Gefitinib 250 mg daily Vandetanib 300 mg daily	PR: 1% PR: 8%	8.1 Weeks 11 Weeks HR: 0.69; 95% CI: 0.50 to 0.9 (p=0.025)	No advantage seen HR: 1.19; 95% CI: 0.84 to 1.68 (p=0.34)
Schiller *et al.*, 2010[73] (Arq 197–209, phase II, abstract)	84		Erlotinib 150 mg daily plus ARQ197 (dose not given)	Not reported	16.1 Weeks	Not reported
	83		Erlotinib 150 mg daily plus placebo		9.7 Weeks HR: 0.81; 95% CI: 0.57 to 1.15 (p=0.23)	
Han *et al.*, 2011[74] (phase II)	54 52		Gefitinib 250 mg daily Gefitinib 250 mg daily plus simvastatin 40 mg daily	31.5% 38.5%	1.9 Months 3.3 Months HR: 0.891; 95% CI: 0.604 to 1.315 (p=0.491)	12 Months 13.6 Months HR: 0.876; 95% CI: 0.567 to 1.354 (p=0.491)
Herbst *et al.*, 2011[75] (BeTa, phase III)	317	313	Erlotinib 150 mg daily plus placebo	19 (6%)	1.7 Months IQR: 1.3–4.1	9.2 Months 40.7% (1-year)
	319	313	Bevacizumab 15 mg/kg plus erlotinib 150 mg daily	38 (13%)	3.4 Months IQR: 1.4–8.4 HR: 0.62; 95% CI: 0.52 to 0.75	9.3 Months 42.1% (1-year) HR: 0.97; 95% CI: 0.80 to 1.18 (p=0.7583)

TABLE V Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Natale *et al.*, 2011[76]	617	614	Erlotinib 150 mg daily	12%	2.0 Months	7.8 Months
(phase III)	623	623	Vandetanib 300 mg daily	12%	2.6 Months	6.9 Months
				(p=0.98)	HR: 0.98;	HR: 1.01;
					95% CI: 0.87 to 1.10	95.08% CI: 0.89 to 1.16
					(p=0.721)	(2-sided p=0.830)
Ramalingam *et al.*, 2011[77]	57	57	Erlotinib 150 mg daily plus placebo	8.8%	1.5 Months	8.1 Months
(phase II)				90% CI: 3.5% to 17.6%	90% CI: 1.45 to 2.91 months	90% CI: 4.8 to 10.3 months
	58	57	Erlotinib 150 mg daily plus	8.8%	1.87 Months	8.1 Months
			R15079 mg/kg weekly	90% CI: 2.4% to 15.3%	90% CI: 1.41 to 2.91 months	90% CI: 6 to 10 months
	57	57	Erlotinib 150 mg daily plus	7%	2.7 Months	12.1 Months
			R1507 16 mg/kg weekly	90% CI: 2.4% to 15.3%	90% CI: 2.1 to 3.9 months	90% CI: 7.8 to 15.2 months
Sequist *et al.*, 2011[78]	84		Erlotinib 150 mg daily plus	10%	3.8 Months	8.5 Months
(phase II)			tivantinib 360 mg			
	83		Erlotinib 150 mg daily plus placebo	7%	2.3 Months	6.9 Months
					HR: 0.81;	HR: 0.87;
					95% CI: 0.57 to 1.16	95% CI: 0.59 to 1.27
					(p=0.24)	(p=0.47)
Spigel *et al.*, 2011[79]	112	111	Erlotinib 150 mg daily plus	8%	3.38 Months	7.62 Months
(phase II)			sorafenib 400 mg twice daily		95% CI: 4% to 15%	29% (6-month)
	56	55	Erlotinib 150 mg daily plus placebo	11%	1.94 Months	7.23 Months
					95% CI: 4% to 22%	22% (6-month)
					HR: 0.86;	HR: 0.89;
					95% CI: 0.60 to 1.22	95% CI: 0.59 to 1.34
					(1-sided p=0.196)	(1-sided p=0.290)
Gian *et al.*, 2012[80]	24		Erlotinib 150 mg daily plus	Not reported	3.1 Months	Not reported
(phase II, abstract)			sorafenib 400 mg twice daily		95% CI: 1.7 to 3.7 months	
	28		Sorafenib 400 mg twice daily		2.3 Months	
					95% CI: 1.7 to 3.6 months	
					(p=0.84)	
Reckamp *et al.*, 2012[81]	54		Erlotinib 150 mg daily plus	Not reported	5.4 Months	Not reported
(phase II, abstract)			high-dose celecoxib 600 mg twice daily			
	53		Erlotinib 150 mg daily plus placebo		2.9 Months	
					(p=0.31)	

TABLE V Continued

Reference (study details)	Patients (*n*)		Treatment	Response rate (CR+PR)	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Scagliotti *et al.*, 2012[82] (phase III)	480		Erlotinib 150 mg daily plus sunitinib 37.5 mg daily	10.6%	3.6 Months	9.0 Months
	480		Erlotinib 150 mg daily plus placebo	6.9% (*p*=0.0471)	2.0 Months HR: 0.807; 95% CI: 0.695 to 0.937	8.5 Months HR 0.922; 95% CI: 0.797 to 1.067 (*p*=0.1388)
Witta *et al.*, 2012[83] (phase II)	65		Erlotinib 150 mg daily plus placebo	9.2%	1.88 Months	6.7 Months
	67		Erlotinib 150 mg daily plus entinostat 10 mg	3.0%	1.97 Months HR: 0.99; 95% CI: 0.68 to 1.44 (*p*=0.98)	8.9 Months HR: 0.85; 95% CI: 0.59 to 1.23 (*p*=0.39)
Besse *et al.*, 2013[84] (phase II)	66		Everolimus 5 mg daily plus erlotinib 150 mg daily	12.1%	2.9 Months 95% CI: 5.4% to 22.5%	9.1 Months 95% CI: 2.4 to 3.9 months
	67		Erlotinib 150 mg daily	10.4%	2.0 Months 95% CI: 4.3% to 20.3%	9.7 Months 95% CI: 1.1 to 2.8 months
Groen *et al.*, 2013[85] (phase II)	65		Sunitinib 37.5 mg daily plus erlotinib 150 mg daily	4.6%	2.8 Months	8.2 Months 95% CI: 5.70 to 11.30 months
	67		Placebo plus erlotinib 150 mg daily	3.0%	2.0 Months HR: 0.898; 80% CI: 0.671 to 1.203 (*p*=0.321)	7.6 Months 95% CI: 5.30 to 13.40 months HR 1.066; 95% CI: 0.705 to 1.612 (*p*=0.617)
Spigel *et al.*, 2013[86] (phase II)	69		Onartuzumab 15 mg/kg plus erlotinib 150 mg daily	5.8%	2.2 Months	8.9 Months
	68		Erlotinib 150 mg daily plus placebo	4.4%	2.6 Months HR: 1.09 (*p*=0.69)	7.4 Months HR: 0.80 (*p*=0.34)

CR = complete response; PR = partial response; TTP = time to progression; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; IQR = interquartile range.

TABLE VI Other second-line epidermal growth factor receptor (EGFR) inhibitor trials in unselected patients

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor plus chemotherapy compared with chemotherapy alone in unselected patients						
Von Pawel *et al.*, 2011[87] (phase II, abstract)	86		Pemetrexed 500 mg/m^2	10.8%	2.9 Months 95% CI: 1.9 to 3.4 months	7.8 Months 95% CI: 5.3 to 10.4 months
	79		Pemetrexed 500 mg/m^2 plus erlotinib 150 mg daily	17.1%	3.2 Months 95% CI: 2.9 to 4.7 months HR: 0.63; 95% CI: 0.44 to 0.9 (p=0.005)	11.8 Months 95% CI: 8.2 to 16.7 months HR 0.68; 95% CI: 0.47 to 0.098 (p=0.019)
Second-line EGFR inhibitor compared with placebo in unselected patients						
Shepherd *et al.*, 2005[7] (BR.21, phase III)	488	488	Erlotinib 150 mg daily	8.9%	2.2 Months	6.7 Months/31%
	243	243	Placebo	<1% (p<0.001)	1.8 Months HR: 0.61; 95% CI: 0.51 to 0.7 (p<0.001)	4.7 Months/22% HR: 0.70; 95% CI: 0.58 to 0.85 (p<0.001)
Thatcher *et al.*, 2005[88] (ISEL, phase III)	1129		Gefitinib 250 mg daily	8.0%	7.2 Months	5.6 Months
	563		Placebo	1.3% (p<0.0001)	2.6 Months (median time to treatment failure)	5.1 Months HR: 0.89; 95% CI: 0.77 to 1.02 (log rank p=0.087)
Gaafar *et al.*, 2011[89] (EORTC 08021/ILCP 01/03, phase III)	86		Gefitinib 250 mg daily	Not reported	4.1 Months	10.9 Months 95% CI: 9.2 to 13.8 months (after 41 months)
	87		Placebo		2.9 Months HR: 0.61; 95% CI: 0.45 to 0.83 (p=0.002)	9.4 Months 95% CI: 6.6 to 13.8 months HR: 0.81; 95% CI: 0.59 to 1.12 (p=0.204)
Second-line EGFR inhibitor compared with EGFR inhibitor in unselected patients						
Fukuoda *et al.*, 2003[91] (IDEAL1, phase II)	104	103	Gefitinib 250 mg daily	17.5%	2.7 Months	7.6 Months 95% CI: 5.3 to 10.1 months 35% (1-year)
	106	106	Gefitinib 500 mg daily	19%	2.8 Months	8.0 Months 95% CI: 6.7 to 9.9 months 29% (1-year)

TABLE VI Continued

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with EGFR inhibitor in unselected patients						
Kris *et al.*, 2003[92]	106	102	Gefitinib 250 mg daily plus placebo	12% (12/102)	Not reported	7 Months
(IDEAL2, phase II)				95% CI: 6% to 20%		27% (1-year projected)
	115	114	Gefitinib 500 mg daily (2×250 mg)	9% (10/114)		6 Months
				95% CI: 4% to 16%		(*p*=0.40)
				(*p*=0.51)		24% (1-year projected)
						(*p*=0.54)
Ahn *et al.*, 2010[93]	48		Erlotinib 150 mg daily	39.6%	3.1 Months	Not reported
(phase II, abstract)	48		Gefitinib 250 mg daily	47.9%	4.9 Months	
				(*p*=0.411)	HR: 0.81;	
					95% CI: 0.52 to 1.25	
					(*p*=0.336)	
Ramalingam *et al.*, 2012[94]	94		Dacomitinib 45 mg daily	17.0%	2.86 Months	9.53 Months
(phase II)	94		Erlotinib 150 mg daily	5.3%	1.91 Months	7.44 Months
				(*p*=0.011)	HR: 0.66;	HR: 0.80;
					95% CI: 0.47 to 0.91	95% CI: 0.56 to 1.1
					(*p*=0.012)	(*p*=0.205)
Shi *et al.*, 2013[95]	200		Icotinib 125 mg three times daily	ORR: 27.6%	4.6 Months	13.3 Months
(ICOGEN, phase III)					95% CI: 3.5 to 6.3 months	
	199		Gefitinib 250 mg daily	ORR: 27.2%	3.4 Months	13.9 Months
					95% CI: 2.3 to 3.8 months	HR: 1.02;
					HR 0.84;	95% CI: 0.82 to 1.27
					95% CI: 0.67 to 1.0	(*p*=0.57)
					(*p*=0.13)	

CR = complete response; PR = partial response; CI = confidence interval; HR = hazard ratio; ORR = overall response rate.

TABLE VII Second-line epidermal growth factor receptor (EGFR) inhibitor trials in clinically selected populations

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Survival	
	Enrolled	Analyzed			Median PFS	Other
Second-line EGFR inhibitor compared with chemotherapy in clinically selected patients						
Ahn *et al.,* 2011[96] (KCSG-LU08–01, phase III, abstract)	135 (not broken down)		Gefitinib 250 mg daily Pemetrexed 500 mg/m^2	ORR: 30.1% ORR: 14.9% (p<0.001)	9.4 Months 2.9 Months (p=0.010)	73.6% (1-year) 70.5% (1-year) (p=0.89)
Lee *et al.,* 2013[97] (phase II)	78		(A) Erlotinib 150 mg daily plus pemetrexed 500 mg/m^2	7.4 Months	20.5 Months	
	82		(B) Erlotinib 150 mg daily	3.8 Months	22.8 Months	
	80		(C) Pemetrexed 500 mg/m^2	4.4 Months A vs. B+C: HR: 0.57; 95% CI: 0.40 to 0.81 (p=0.002)	17.7 Months A vs. B+C: HR: 1.08; 95% CI: 0.69 to 1.67 (p=0.747)	
Yang *et al.,* 2013[98] (CTONG 0806, phase II, abstract)	81 76		Gefitinib 250 mg daily Pemetrexed 500 mg/m^2	14.7% 13.3% (p=0.814)	1.6 Months 4.8 Months HR: 0.51; 95% CI: 0.36 to 0.73 (p<0.001)	Overall survival not yet mature
Third- or fourth-line EGFR inhibitor compared with placebo in clinically selected patients						
Miller *et al.,* 2012[99] (LUX-Lung1, phase IIB/III)	390 195		Afatinib 50 mg daily plus BSC Placebo plus BSC	7% 0.5%	3.3 Months 1.1 Months HR: 0.38; 95% CI: 0.31 to 0.48 (p<0.0001)	10.8 Months 12.0 Months HR: 1.08; 95% CI: 0.86 to 1.35 (p=0.74)

CR = complete response; PR = partial response; PFS = progression-free survival; ORR = overall response rate; HR = hazard ratio; CI = confidence interval; BSC = best supportive care.

and, in a selected population of patients, also gefitinib or erlotinib (Table VII). The response rates were 7% for afatinib and 0.5% for placebo. A significant improvement in PFS was evident for patients randomized to afatinib (3.3 months vs. 1.1 months, $p < 0.0001$). However, no difference in the primary outcome of OS was observed (10.8 months vs. 12 months, $p = 0.74$). Adverse effects were consistent with those associated with EGFR inhibitors[99]. There is therefore currently no evidence that further therapy with an EGFR TKI in patients who have already received gefitinib or erlotinib improves OS.

Molecularly Selected Populations: *EGFR Inhibitor Compared with Chemotherapy:* One study compared the use of an EGFR inhibitor with the use of chemotherapy in patients known to be *EGFR* wild-type[100]. The trial specifically excluded crossover to the other treatment at the time of progression. Compared with erlotinib, docetaxel was associated with an improved PFS (HR: 0.71; 95% CI: 0.53 to 0.95; $p = 0.02$). The primary outcome in the trial was OS, which was also significant for docetaxel at 8.2 months compared with 5.4 months for erlotinib (HR: 0.73; 95% CI: 0.53 to 1.00; $p = 0.05$; Table VIII)[100].

EGFR Inhibitor Plus Another Agent Compared with an EGFR Inhibitor: Two studies examined the use of an EGFR inhibitor plus another agent compared with erlotinib alone in molecularly selected patients[101,102] (Table VIII). Time to progression was significantly longer with erlotinib and apricoxib ($p = 0.018$) in the Gitlitz *et al.* trial[101], but no different in the Belani *et al.* trial[102]. However, OS favoured the erlotinib and placebo group (HR: 0.4; $p = 0.025$) in the Gitlitz *et al.* trial[101]. Again, no difference was seen between the groups in the Belani *et al.* trial[102]. Adverse effects were in line with those associated with EGFR inhibitors.

EGFR Inhibitor Compared with EGFR Inhibitor: One study compared EGFR inhibitors in molecularly selected patients[103] (Table VIII). Response rate and PFS were higher in the gefitinib group than in the erlotinib group. Significance was not reached for PFS ($p = 0.336$). Adverse effects were in line with those associated with EGFR inhibitors[103].

Maintenance

Unselected Populations: *EGFR Inhibitors:* In recent years, attempts to improve the survival of patients with advanced NSCLC have led to considerable interest in

TABLE VIII Second-line epidermal growth factor receptor (EGFR) inhibitor trials in molecularly selected populations

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with chemotherapy in molecularly selected patients						
Garassino *et al.*, 2013[100] (TAILOR, phase III)	112		Erlotinib 150 mg daily	Not reported	2.4 Months	5.4 Months
	110		Docetaxel 75 mg/m^2		2.9 Months HR: 0.71; 95% CI: 0.53 to 0.95 (p=0.02)	8.2 Months HR: 0.73; 95% CI: 0.53 to 1.00 (p=0.05)
Second-line EGFR inhibitor plus another agent compared with EGFR inhibitor in molecularly selected patients						
Gitlitz *et al.*, 2011[101] (APRICOT-L, phase II, abstract)	120		Erlotinib 150 mg daily plus apricoxib 400 mg daily	Not reported	TTP: 2.1 months	5.6 Months
	176		Placebo plus erlotinib 150 mg daily		TTP: 1.8 months HR: 0.5 (p=0.018)	5.9 Months HR: 0.4 (p=0.025)
Belani *et al.*, 2013[102] (phase II)	18		PF-3512676 (0.20 mg/kg) plus erlotinib 150 mg daily	Not reported	1.6 Months	6.4 Months
	21		Erlotinib 150 mg daily		1.7 Months HR: 1.00; 95% CI: 0.5 to 2.0 (p=0.9335)	4.7 Months HR: 1.3; 95% CI: 0.6 to 2.8 (p=0.4925)
Second-line EGFR inhibitor compared with EGFR inhibitor in molecularly selected patients						
Kim *et al.*, 2012[103] (phase II)	48		Gefitinib 250 mg daily	47.9%	4.9 Months	Not reached
	48		Erlotinib 150 mg daily	39.6%	3.1 Months (p=0.336)	

CR = complete response; PR = partial response; HR = hazard ratio; CI = confidence interval; TTP = time to progression.

evaluating maintenance therapies. Trials have evaluated continuing a drug ("continuation maintenance") or switching to another drug ("switch maintenance"). Five studies have examined EGFR inhibitors in unselected patients in the switch-maintenance setting, but none of those trials mandated the use of an EGFR TKI in the placebo arm at the time of disease progression.

One study compared an EGFR inhibitor with chemotherapy in the maintenance setting (Table IX). Bylicki *et al.*[107] randomized patients to maintenance therapy with erlotinib, gemcitabine, or observation. In the observation group, patients received no treatment. No clear improvement in PFS was observed for either erlotinib or gemcitabine. No significant difference in OS was observed, but a trend toward improved survival was evident in both the erlotinib group (HR: 0.80; 95% CI: 0.61 to 1.05; $p = 0.13$) and the gemcitabine group (HR: 0.81; 95% CI: 0.61 to 1.07; $p = 0.109$) compared with the observation group. No outstanding adverse effects occurred in the erlotinib group[107].

Four trials evaluated an EGFR TKI as maintenance therapy. A clear improvement in PFS was observed, but only one trial showed a significant improvement in OS. One Japanese trial compared 6 cycles of a platinum doublet with 3 cycles of a platinum doublet followed by gefitinib until progression. A significant improvement in PFS was observed, but no significant improvement in OS[105]. A second trial compared bevacizumab plus erlotinib with bevacizumab alone in patients treated with 4 cycles of carboplatin, paclitaxel, and bevacizumab. A significant improvement in PFS (4.8 months vs. 3.7 months, $p < 0.001$) was observed[108]. Two additional studies evaluated an EGFR TKI as maintenance therapy, comparing it with a placebo control, after 4 cycles of a platinum doublet. Both studies showed significant improvements in PFS. The SATURN trial, which evaluated maintenance erlotinib, showed a significant improvement in OS, although the difference in median survival was only 1 month[104]. In a preplanned subgroup analysis of the SATURN trial, patients with stable disease after first-line chemotherapy experienced a greater OS benefit with maintenance erlotinib (median survival: 11.9 months for erlotinib vs. 9.6 months for placebo; HR: 0.72; 95% CI: 0.59 to 0.89; $p = 0.0019$) than did patients who experienced a previous complete or partial response (12.5 months for erlotinib vs. 12.0 months for placebo; HR: 0.94; 95% CI: 0.74 to 1.20; $p = 0.618$)[104]. Zhang *et al.*[106] showed a similar effect on OS with maintenance gefitinib, although the difference was not statistically significant (HR: 0.84; 95% CI: 0.62 to 1.14).

Quality of life and adverse effects were assessed in two studies. The SATURN study showed no statistically significant difference in quality of life (FACT-L questionnaire)

TABLE IX Epidermal growth factor receptor (EGFR) inhibitors compared with chemotherapy in the maintenance setting

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
EGFR inhibitors in unselected patients in the maintenance setting						
Cappuzzo *et al.,* 2010[104] (SATURN, phase III)	438	437	Erlotinib 150 mg day	11.9%	12.3 Weeks 25% (6-month) 95% CI: 21% to 29%	12 Months
	451	447	Placebo	5.4% (p=0.0006)	11.1 Weeks 15% (6-month) 95% CI: 12% to 19% HR: 0.71; 95% CI: 0.62 to 0.82 (p<0.0001)	11 Months HR: 0.81; 95% CI: 0.70 to 0.95 (p=0.0088)
Takeda *et al.,* 2010[105] (WJTOG 0203, phase III)	302	298	Chemotherapy[a] plus gefitinib 250 mg daily	34.2%	4.6 Months	13.7 Months
	301	297	Chemotherapy[a]	29.3% (p=0.20)	4.3 Months HR: 0.68; 95% CI: 0.57 to 0.80 (p<0.001)	12.9 Months
Zhang *et al.,* 2012[106] (phase III)	148		Gefitinib 250 mg daily	24%	4.8 Months	18.7 Months
	148		Placebo	1% OR: 54.10 95% CI: 7.17 to 408 (p=0.0001)	2.6 Months HR: 0.42; 95% CI: 0.33 to 0.55 (p<0.0001)	16.9 Months HR: 0.84; 95% CI: 0.62 to 1.14 (p=0.26)
Bylicki *et al.,* 2013[107] (IFCT-GFPC 05–02, phase II)	155		(A) Erlotinib 150 mg daily	14%	A vs. C: 4.2 vs. 3.9 months; HR: 0.83; 95% CI: 0.64 to 1.09 B vs. C: 4.2 vs. 3.9 months; HR: 0.81; 95% CI: 0.62 to 1.06	9.1 Months
	154		(B) Gemcitabine 1250 mg/m^2	6%		8.3 Months
	155		(C) Observation	14%		7.5 Months A vs. C: HR: 0.80; 95% CI: 0.61 to 1.05 (p=0.13) B vs. C: HR: 0.81; 95% CI: 0.61 to 1.07 (p=0.109)
Johnson *et al.,* 2013[108] (ATLAS, phase II)	370		Erlotinib 150 mg daily plus bevacizumab 15 mg/kg	Not reported	4.8 Months	14.4 Months
	373		Bevacizumab 15 mg/kg		3.7 Months HR: 0.708; 95% CI: 0.580 to 0.864 (p<0.001)	13.3 Months HR: 0.917; 95% CI: 0.698 to 1.205 (p=0.5341)
EGFR inhibitor in clinically selected patients in the maintenance setting						
Ahn *et al.,* 2012[109] (phase II)	25		Gefitinib 250 mg daily	46.2%	HR: 0.191; 95% CI: 0.074 to 0.0497	80.6% (6-month) 74.8% (12-month) 59.5% (24-month)
	24		Pemetrexed 500 mg/m^2 with optional cisplatin 75 mg/m^2	35.5% OR: 1.56; 95% CI: 0.59 to 4.10 (p=0.369)		93.3% (6-month) 93.3% (12-month) 77.4% (24-month) HR: 2.151; 95% CI: 0.826 to 5.599

[a] Carboplatin AUC 6 plus (paclitaxel 200 mg/m^2 or cisplatin 80 mg/m^2) plus (irinotecan 60 mg/m^2 or cisplatin 80 mg/m^2) plus (vinorelbine 25 mg/m^2 or cisplatin 80 mg/m^2) plus (gemcitabine 1000 mg/m^2 or cisplatin 80 mg/m^2) plus docetaxel 60 mg/m^2.

CR = complete response; PR = partial response; AUC = area under the curve; HR = hazard ratio; CI = confidence interval; OR = odds ratio.

between patients receiving erlotinib and those receiving placebo (HR for time to deterioration in quality of life: 0.96; 95% CI: 0.79 to 1.16). A *post hoc* analysis showed that time to pain (HR: 0.61; 95% CI: 0.42 to 0.88; $p = 0.008$) and time to analgesic use (HR: 0.66; 95% CI: 0.46 to 0.94; $p = 0.02$) were both significantly improved with erlotinib[104]. The Zhang *et al.*[106] 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.

Adverse effects were consistent with what would be expected for gefitinib and erlotinib (increase in rash and diarrhea).

Clinically Selected Populations: *EGFR Inhibitors:* One fully published study[109] examined the use of an EGFR inhibitor in clinically selected patients in the maintenance setting. Table IX presents the study characteristics.

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

DISCUSSION AND CONCLUSIONS

Analysis of early trials evaluating EGFR TKIs suggested that clinical characteristics such as Asian ethnicity, female sex, non-smoking status, and adenocarcinoma were associated with a higher likelihood of response. Those characteristics were subsequently used in clinical trials to enrich the population of patients who might benefit from those 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. The present systematic review provides guidance for 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, data about the efficacy of EGFR TKIs compared with the efficacy of platinum-based chemotherapy are inconsistent. The largest trial in that setting, TORCH[13], showed a statistically significantly inferior OS for patients receiving first-line EGFR TKI therapy, and those agents are therefore 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 have also had mixed results. Although selection strategies are designed to increase the proportion of patients with an *EGFR* mutation, data from the IPASS trial show that, when clinical characteristics are used to select patients, only 60% typically have *EGFR* mutations[36]. Significantly worse response rates and PFS are observed for patients with wild-type *EGFR* who are treated with first-line gefitinib. The use of clinical characteristics such as ethnicity, sex, smoking status, and histology cannot therefore be recommended in selecting patients for first-line therapy with an EGFR TKI. No available data support combining an EGFR TKI with platinum-based chemotherapy. However, high-quality evidence from multiple randomized clinical trials shows that an EGFR TKI is the preferred initial therapy (in preference to a platinum doublet) for patients with an activating mutation of the *EGFR* gene. Such treatment is associated with a higher likelihood of response, longer PFS, and improved quality of life, but with no clear difference in OS. Many patients randomized in the trials to platinum-doublet chemotherapy crossed over to an EGFR TKI as subsequent therapy. The likely effect of that crossover was to dilute any survival difference between the groups, making comparisons of OS less informative.

Cohort data from the Spanish Lung Cancer Group[30] report on EGFR TKIs given as either first- or second-line therapy in patients with *EGFR* mutations. The benefit appears to be similar in both groups, so that even though the comparison was nonrandomized, the consensus is that crossover explains the difference. Although the trials show statistical heterogeneity, no available data suggest that one EGFR TKI is superior to another in this setting. Some trials included only patients with exon 19 deletion and exon 21 L858R point mutation; other trials such as LUX-Lung 3 included other less common mutations. Those considerations might be a factor in making a choice of agent. However, the decision to use gefitinib, erlotinib, or afatinib is largely influenced by concerns about their toxicity or cost.

Data from the NCIC BR.21 trial of erlotinib compared with placebo demonstrate a modest improvement in survival and quality of life with erlotinib in patients who are no longer candidates for further chemotherapy[7]. Based on those data, erlotinib was recommended as a last line of therapy in the previous version of this guideline. However, multiple trials of second-line therapy comparing an EGFR TKI with chemotherapy have now been reported. A meta-analysis of the data demonstrates similar PFS and OS. Level 1 evidence therefore now shows that 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 OS on an EGFR TKI or second-line chemotherapy[55]. It is therefore 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[100] trial, performed only in patients with wild-type *EGFR*, demonstrated improved PFS and OS when patients received docetaxel chemotherapy (compared with erlotinib). That trial did not allow crossover between the treatment arms, thus denying patients a previously established therapy. Those data therefore do not alter treatment recommendations at this time. The data concerning the combination of an EGFR TKI with either chemotherapy or another targeted agent are inconsistent. Some promising data have emerged from randomized phase II trials, but they require confirmation in phase III trials. Combination therapy with an EGFR TKI in the second- or third-line setting is therefore 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. Although data from the LUX-Lung 1 trial demonstrated a significant improvement in PFS in a select subgroup of patients, that trial did not meet its primary objective of improved OS[99]. Given the absence of improved survival, therapy with afatinib after progression on another EGFR TKI is not recommended.

The EGFR TKIs have also been evaluated as switch-maintenance therapy. The SATURN trial demonstrated improved OS in patients receiving maintenance erlotinib[104]. Interestingly, that benefit was observed whether the patients were *EGFR* mutation–positive or *EGFR* wild-type. No molecular marker could identify patients in whom a survival benefit was not observed. The magnitude of the benefit was modest, and other available maintenance therapy strategies should be considered. Nevertheless, there are data to support maintenance therapy with erlotinib after 4 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 *EGF*R wild-type, but it should be administered as second- or third-line therapy.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: PME has received consulting fees from Roche, Boehringer–Ingelheim, and Pfizer. PME is also study chair for the NCIC Clinical Trials Group BR.26, which is comparing dacomitinib with placebo in NSCLC patients who have received prior chemotherapy and an EGFR TKI. RF is a member of the Roche and AstraZeneca boards. The remaining authors declared that they had no conflicts of interest.

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