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Epidermal growth factor receptor tyrosine kinase inhibitors for non-small cell lung cancer

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Abstract

First-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib and erlotinib, have proven to be highly effective agents for advanced non-small cell lung cancer (NSCLC) in patients harboring an activating EGFR mutation such as the exon 19 deletion mutation and L858R. Although those reversible small molecular targeted agents provide a significant response and survival benefit, all responders eventually acquire resistance. Second-generation EGFR-targeting agents, such as irreversible EGFR/HER2 tyrosine kinase inhibitors and pan-HER TKIs, may improve survival further and be useful for patients who acquired resistance to first-generation EGFR-TKIs. This review discusses novel therapeutic strategies for EGFR-mutated advanced NSCLC using first- and second-generation EGFR-TKIs.

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Key words: Epidermal growth factor receptor mutation; Epidermal growth factor receptor tyrosine kinase inhibitors; Non-small cell lung cancer; Secondary resistance

Core tip: Although gefitinib and erlotinib provide a significant response and survival benefit, all responders eventually acquire resistance. Second-generation epidermal growth factor receptor (EGFR)-targeting agents, such as afatinib and dacomitinib, may improve survival further and be useful for patients who acquired resistance to first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). This review discusses novel therapeutic strategies for EGFR-mutated advanced non-small cell lung cancer using first- and second-generation EGFR-TKIs.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) is the founding member of the ErbB family of 4 structurally related receptor tyrosine kinases, including EGFR (ErbB1), ErbB2, ErbB3 and ErbB4. The receptors of the ErbB family are activated after binding to peptide growth factors of the EGF family. Upon ligand binding, the ErbB receptors form either homo- or heterodimers and, after dimerization, auto- and transphosphorylation on tyrosine residues of the ErbB receptors occurs^[1]. Non-small cell lung cancer (NSCLC) tumors harboring specific EGFR mutations are dependent on EGFR signaling for uncontrolled proliferation and resistance to apoptosis^[2-4] (Figure 1). The 2 most frequent activating EGFR mutations, responsible for approximately 90% of this anomaly in the cell cycle, are the L858R point mutation and the exon

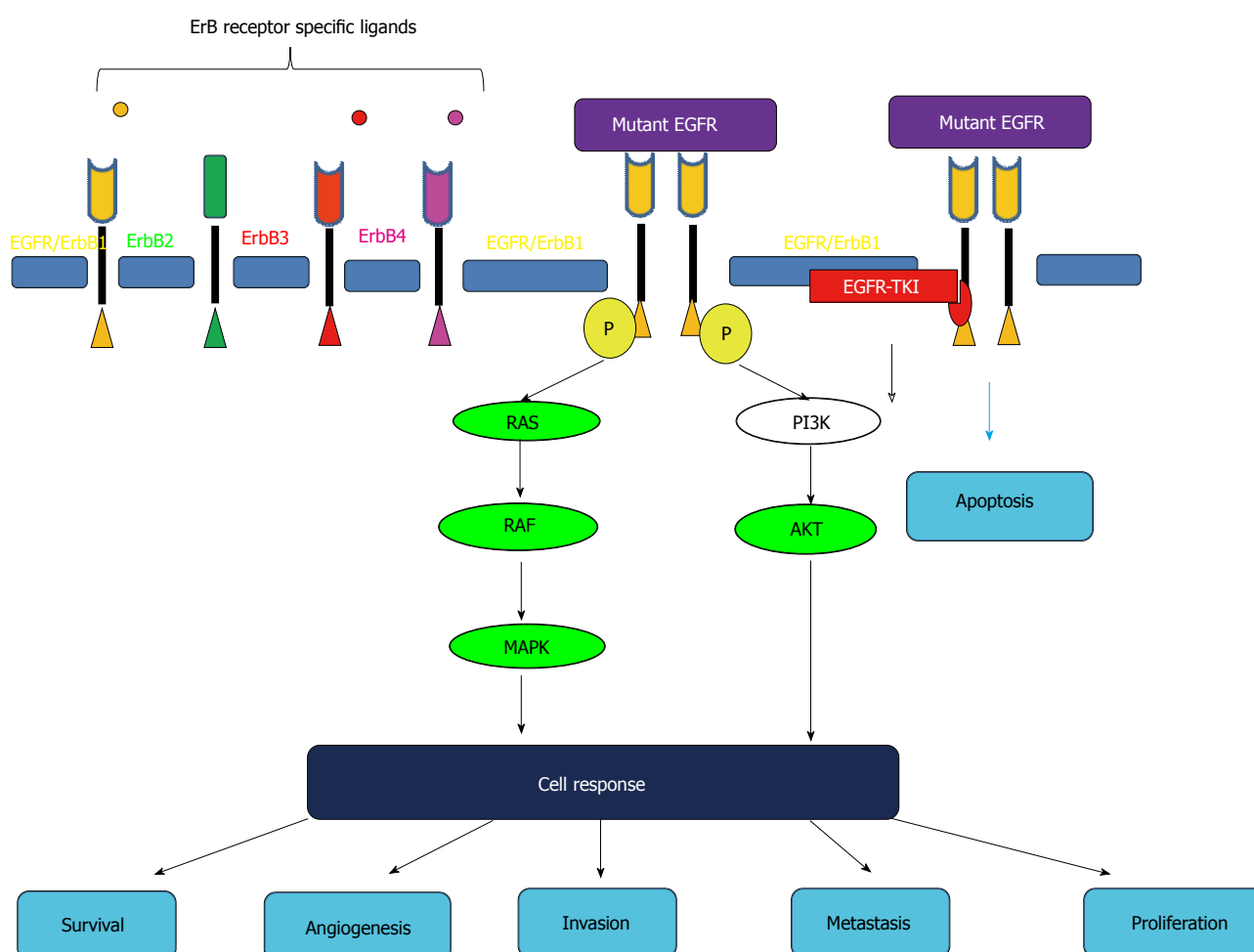


Figure 1 Cell-proliferative signaling pathways in lung cancer cell. The epidermal growth factor receptor (EGFR) family consists of 4 members: EGFR/ErbB1, ErbB2, ErbB3 and ErbB4. Specific ligands (e.g., EGF, TGF- α) binding to EGFR results in a conformational change of the receptor, exposing the dimerization domain and allowing for homodimerization with a second EGFR, or heterodimerization with another member of the EGFR family. Activation of the EGFR results in autophosphorylation of key tyrosine residues. These tyrosine phosphorylated sites leads to the activation of major downstream signaling cascades, including the Ras/Raf/MAPK pathway and PI3K/AKT pathway. These pathways act in a coordinated manner to promote cell survival. While wild type EGFR is activated in a ligand-dependent manner, mutant EGFR is constitutively activated. First- or second-generation EGFR-TKIs bind reversibly or irreversibly to the kinase domain and effectively inhibit EGFR tyrosine kinase by binding to the adenosine triphosphate-binding site of the enzyme and inhibit downstream signaling, leading to apoptosis of cancer cells.

19 deletion mutation^[5]. In the last decade, therapeutic agents targeting the EGFR signaling pathway, including 2 reversible EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, have been clinically effective in treating lung cancer patients harboring activating EGFR mutations^[6-12].

Despite the great efficacy of first-generation EGFR-TKIs in patients with EGFR-mutated NSCLC, all responders eventually develop resistance to these agents. The treatment strategies for NSCLC patients who developed resistance to first-generation EGFR-TKIs are actively studied. Recently, second-generation EGFR-TKIs, including afatinib (BIBW 2992) and dacomitinib (PF-00299804), became available; these drugs are intended to further prolong survival in patients harboring activating EGFR mutation and may overcome the resistance to first-generation EGFR-TKIs. This article focuses on the EGFR-TKI-based strategy for patients with advanced NSCLC expressing activated mutant EGFR.

STANDARD PLATINUM-BASED CHEMOTHERAPY VS FIRST-GENERATION EGFR-TKIS AS A FIRST-LINE TREATMENT OF EGFR-MUTATED NSCLC

Efficacy and toxicity

Four previous randomized phase III trials assessing first-line treatment demonstrated a significantly higher response rate (RR) and longer progression-free survival (PFS) in patients treated with first-generation EGFR-TKIs, including gefitinib and erlotinib, than in patients treated with standard platinum-based combination chemotherapy (Table 1). Although these trials met their primary endpoint with statistically significant longer PFS, no significant difference was observed in terms of overall survival (OS). No restrictions were imposed on treatment after the end of protocol therapy in these 4 trials and the majority of patients in the control arm received EGFR-

Table 1 Randomized phase III trials comparing first-generation epidermal growth factor receptor-tyrosine kinase inhibitors to platinum-based combination chemotherapy as a first-line treatment in patients with epidermal growth factor receptor-mutated non-small cell lung cancer

Ref.	Treatment	Number of patients	Age	Response rate	Median PFS (mo)	Median OS (mo)
WJTOG3405 ^[9]	gefitinib	86	< 75	62%	9.2	35.5
	CDDP + TXT	86		32%	6.3	38.8
					HR, 0.48; <i>P</i> < 0.001	HR, 1.64; <i>P</i> = 0.211
NEJ002 ^[10]	gefitinib	114	< 75	74%	10.8	30.5
	CBDCA + PTX	114		31%	5.4	23.6
					HR, 0.30; <i>P</i> < 0.001	HR, 0.89; NS
OPTIMAL ^[11]	erlotinib	82	≥ 18	83%	13.1	22.7
	CBDCA + GEM	72		36%	4.6	28.9
					HR, 0.16; <i>P</i> < 0.001	HR, 1.04 NS
EURTAC ^[12]	erlotinib	86	≥ 18	58%	9.7	19.3
	Platinum + TXT/GEM	87		15%	5.2	19.5
					HR, 0.37; <i>P</i> < 0.001	HR, 1.04; NS

EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; PFS: Progression-free survival; OS: Overall survival; CDDP: Cisplatin; TXT: Docetaxel; PTX: Paclitaxel; GEM: Gemcitabine; CBDCA: Carboplatin; NR: Not reached; HR: Hazard ratio; NS: Not significant.

TKI therapy at least once.

In these 4 randomized phase III trials, severe adverse events or treatment-related toxicity leading to discontinuation of the therapy were significantly less prevalent in patients treated with first-generation EGFR-TKIs compared to standard chemotherapy. The most common adverse events in patients treated with first-generation EGFR-TKIs were cutaneous toxicity, including skin rash and dry skin, diarrhea and elevated transaminase level. Compared to chemotherapy, hematological toxicity, fatigue, alopecia and nausea were less prevalent in the experimental arm of first-generation EGFR-TKIs^[9-12].

Quality of life

Three randomized phase III trials comparing first-generation EGFR-TKIs to standard chemotherapy have shown EGFR-TKI to be superior to chemotherapy in quality of life (QoL) effects. Two randomized phase III trials of first-generation EGFR-TKIs, including the IPASS study^[7] and OPTIMAL study^[13], assessed QoL as a secondary endpoint using Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI), or Lung Cancer-Specific Subscale (LCS; Table 2). Patients receiving first-line EGFR-TKIs experienced clinically relevant improvements in QoL compared to patients treated with standard platinum doublet chemotherapy in these studies. Among patients harboring activating EGFR mutations in the IPASS study, significant improvement of QoL was found in patients treated with gefitinib compared to patients treated with chemotherapy. Furthermore, rapid improvement of QoL both in terms of FACT-L and LCS was observed in patients with mutated EGFR. In the OPTIMAL study, patients with an improvement in QoL showed improved PFS compared with patients with stable or worsened QoL. Further significant correlations were observed between improved QoL and tumor re-

sponse with FACT-L, TOI and LCS.

In the NEJ 002 study, QoL was assessed by analyzing time to deterioration from baseline in the physical, mental and life well-being QoL scales. Time to defined deterioration in physical and life well-being significantly favored gefitinib over standard chemotherapy [hazard ratio (HR) of time to deterioration, 0.34; 95% confidence interval (CI), 0.23-0.50; $P < 0.0001$ and HR, 0.43; 95%CI: 0.28-0.65, $P < 0.0001$ respectively]^[14].

FIRST-GENERATION EGFR-TKIS FOR ELDERLY PATIENTS AND/OR PATIENTS WITH POOR PS (3-4)

In the WJOG 3405 study and the NEJ 002 study, patients of older age (≥ 75) and poor performance status (PS 2-4) were excluded. An earlier phase II trial demonstrated efficacy of gefitinib as a first-line treatment in elderly patients with activated mutant EGFR and/or patients with poor PS (3-4; Table 3)^[15-17]. Although each trial had a small sample size and was a single-arm phase II trial, high RRs (59%-74%) and long PFSs were observed. Inoue *et al.*^[15] reported utility of first-line gefitinib for extremely poor PS patients and approximately 80% of the patients enrolled this trial improved PS after initiation of gefitinib. Among them, some patients with PS = 4 experienced a dramatic improvement in systemic advanced disease shortly after initiation of gefitinib. No prospective clinical trials of gefitinib except for this study in advanced NSCLC patients with poor PS (3-4) have been conducted and there have been no randomized trials comparing EGFR-TKIs to chemotherapy as a first-line treatment of EGFR-mutated advanced NSCLC.

Although no randomized controlled trials of erlotinib in elderly patients harboring an activating EGFR

Table 2 Quality of life assessment (first-generation epidermal growth factor receptor-tyrosine kinase inhibitors vs chemotherapy)

Study	Treatment	Method ^a					
		FACT-L	P ^b	TOI	LCS	P	
IPASS ^[7]	Gefitinib	70.2%	< 0.0001	70.2%	< 0.0001	75.6%	0.000
	CBDCA + PTX	44.5%		38.3%		53.9%	
OPTIMAL ^[13]	Erlotinib	74.3%	< 0.0001	73%	< 0.0001	77%	< 0.0001
	CBDCA + GEM	31.5%		25.9%		31.5%	

^aEvaluable for quality of life population; logistic regression model with covariates; ^b6-point improvement (FACT-L and TOI); 2-point improvement (LCS), maintained ≥ 21 d. EGFR-TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; FACT-L: Functional assessment of cancer therapy-lung; TOI: Trial outcome index; LCS: Lung cancer subscale; CBDCA: Carboplatin; PTX: Paclitaxel; GEM: Gemcitabine.

Table 3 Phase II trials of gefitinib in elderly patients with activated mutant epidermal growth factor receptor and in patients with poorer performance status

Ref.	Number of patients	Age	PS	Response rate	Median PFS (mo)	Median OS (mo)
Inoue <i>et al</i> ^[15]	29	50 \leq	1-4 ^a	66%	6.5	17.8
Asami <i>et al</i> ^[16]	17	75 \leq	0-1	59%	12.9	27.4
Maemondo <i>et al</i> ^[17]	31	75 \leq	0-1	74%	12.8	33.8

^aPatients with PS (1-2) were all 80 yr or older. PS: Performance status; PFS: Progression-free survival; OS: Overall survival.

Table 4 Clinical trials of first-generation epidermal growth factor receptor tyrosine kinase inhibitors in patients with epidermal growth factor receptor-mutated non-small cell lung cancer who failed chemotherapy

Ref.	EGFR-TKI	Number of patients	Response rate	Time to progression (mo)
Sutani <i>et al</i> ^[21]	Gefitinib	23	74%	9.4
Han <i>et al</i> ^[22]	Gefitinib	17	64%	21.7
Cortes-Funes <i>et al</i> ^[23]	Gefitinib	10	60%	12.3
Kim <i>et al</i> ^[24]	Erlotinib	8	63%	NR
Ahn <i>et al</i> ^[25]	Erlotinib	78	58%	8.6

EGFR-TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC: Non-small cell lung cancer; NR: Not reached.

mutation have been conducted yet, 18 years old or older patients were enrolled in the OPTIMAL study and the EUROTAC study. No negative effects of erlotinib, such as severe toxicity, lower response and shorter survival, were documented in elderly patients in these studies. Another phase II trial showed that erlotinib is effective and relatively well tolerated in chemotherapy-naïve elderly patients (≥ 70) with advanced NSCLC^[18]. EGFR mutations were detected in 9 of 43 patients tested and all patients harboring an EGFR mutation achieved either a partial response (PR) or stable disease (SD).

Reck *et al*^[19] examined a subpopulation of elderly patients (≥ 70) receiving first-line erlotinib ($n = 485$) in the TRUST study ($n = 6580$), an open-label phase IV trial of erlotinib in advanced non-selected NSCLC patients who had previously failed, or were considered unsuitable to receive, standard chemotherapy or radiotherapy^[20]. In this subpopulation, disease control rate (complete response plus PR plus SD), median PFS and OS were 79% (*vs* 69% for the overall TRUST population; $P < 0.0001$), 4.57 mo (*vs* 3.25 mo), and 7.29 mo (*vs* 7.9 mo) respectively. Nev-

ertheless, elderly patients with poor PS (2-3) had worse survival outcomes than those with good PS (0-1). Median PFS of PS 0-1, 2 and 3 were 5.58 mo, 3.15 mo and 1.81 mo respectively. Median OS of PS 0-1 and 3 was 10.38 mo and 2.07 mo respectively. Eighteen percent of elderly patients had an erlotinib-related adverse event (AE) and 20 patients (4%) developed severe toxicity [grade ≥ 3 ; *vs* 173 patients (3%) in the overall TRUST population]. Twenty-seven percent of elderly patients needed a dose reduction of erlotinib (*vs* 17% in the overall TRUST population). No molecular information, including EGFR mutation status, was examined in this study. Considering the results of these studies, investigators concluded that first-line erlotinib may be well tolerated and be considered for elderly patients with advanced NSCLC the same as non-elderly patients.

WHICH LINE OF TREATMENT IS BETTER FOR FIRST-GENERATION EGFR-TKIS IN PATIENTS WITH MUTANT EGFR?

Several investigators have assessed first-generation EGFR-TKIs as a second/third-line treatment in patients with NSCLC carrying activated mutant EGFR based on their small prospective or retrospective studies and subset analysis of phase III trials (Table 4)^[21-25]. As for response rate and time to progression, these results were similar to the results of a previous large phase III trial of first-generation EGFR-TKIs as a first-line treatment. Rosell *et al*^[8] reported that no significant difference was observed between chemotherapy-naïve and chemorefractory patients in terms of RR (73.5% *vs* 67.4%), PFS (14 mo *vs* 13 mo) and OS (28 mo *vs* 27 mo) with erlotinib in patients with activated mutant EGFR.

In contrast, lower RR with gefitinib was documented

in the NEJ 002 study in patients who failed first-line chemotherapy compared to patients treated with gefitinib as a first-line treatment (56% *vs* 74%). Several studies documented that heterogeneity in EGFR gene expression and mutations was observed in patients with NSCLC^[26-28]. Bai *et al*^[29] reported that chemotherapy may reduce EGFR mutation frequency in patients with NSCLC. In their study, samples were derived from 3 cohorts and 409 patients were reviewed. The decrease in EGFR mutation rate was statistically significant and patients whose EGFR mutations switched from positive to negative after chemotherapy had a better RR than patients with a reverse change among the patients who received first-line chemotherapy with matched pre- and post-chemotherapy blood samples. A similar decrease in EGFR mutation rate was observed in tissues after neoadjuvant chemotherapy in the second cohort (34.9% *vs* 19.0%, $P = 0.013$). In the third cohort, 38.0% of the tumors showed intratumor heterogeneity of EGFR mutations, whereas 62.0% were homogeneous, either with an EGFR mutation or no mutation. The authors concluded that chemotherapy may reduce EGFR mutation frequency in patients with NSCLC.

Lee *et al*^[30] reviewed 23 randomized controlled trials comparing EGFR-TKIs or EGFR-TKIs plus chemotherapy to chemotherapy or placebo, including 13 studies as a first-line treatment, 7 as a second-line treatment, and 3 as maintenance therapy ($n = 14570$). Data on PFS were available from 21 trials of EGFR-TKIs, including gefitinib (10 trials), erlotinib (10 trials) and afatinib (1 trial), compared to control treatment. EGFR-TKIs prolonged PFS in patients with mutated EGFR and an EGFR mutation was predictive of PFS in all settings. In EGFR mutation-positive patients, EGFR-TKI treatment was associated with a lower risk of disease progression in first-line settings (HR, 0.43; 95%CI: 0.38 to 0.49, $P < 0.001$) and in second-line or later settings (HR, 0.34; 95%CI: 0.20 to 0.60, $P < 0.001$). This study demonstrates that the magnitude of effect on PFS in patients with mutated EGFR is similar to that in patients receiving EGFR-TKIs as either a first- or second-line treatment (HR, 0.43 and 0.34 respectively). EGFR-TKI treatment, however, had no impact on OS in patients with mutated EGFR.

A recent systematic review of chemotherapy trials for NSCLC indicated that PFS advantage is unlikely to be associated with an OS advantage due to the increasing impact of survival post-progression on OS^[31]. Salvage therapy after disease progression may have a great influence on the prolongation of survival. In randomized phase III trials, including the IPASS study, the WJTOG 3405 study and the OPTIMAL study, a considerable percentage of enrolled patients was not treated with EGFR-TKIs as a salvage therapy because of a patient's refusal and deterioration of the general condition: IPASS (36%), WJTOG3405 (41%) and OPTIMAL (30%). Although a considerable number of patients did not receive EGFR-TKI therapy after failure of standard chemotherapy, no statistically significant difference was noted in terms of overall survival in each trial.

GEFITINIB OR ERLOTINIB AS A FIRST-LINE TREATMENT OF NSCLC POSITIVE FOR AN ACTIVATING EGFR MUTATION

No trials comparing erlotinib directly with gefitinib as a first-line treatment in patients with activated mutant EGFR have been conducted. A retrospective study showed that PFS showed no difference with either agent in patients harboring an EGFR mutation^[32]. Among 224 patients, including 124 treated with gefitinib and 100 treated with erlotinib who were reviewed, 75 patients received EGFR-TKIs as first-line therapy and 146 patients tested positive for an activating EGFR mutation. In patients harboring an EGFR mutation, median RR and PFS with gefitinib and erlotinib was 51%, 10.5 mo ($n = 94$) and 58%, 10.4 mo ($n = 52$) respectively. No statistically significant difference was observed in terms of RR and PFS between patients treated with gefitinib and those treated with erlotinib. HRs for PFSs were 0.32-0.54 in previous randomized phase III trials of gefitinib as a first-line treatment compared to standard chemotherapy, including the IPASS study, First-Signal study^[33], WJTOG 3405 study and the NEJ 002 study.

On the other hand, HRs for PFSs were 0.16-0.37 in a phase III trial of first-line erlotinib, including the OPTIMAL study and EUROTAC study. Schwander *et al*^[34] reported at the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) 2011 Annual International Meeting that erlotinib shows better efficacy as a molecular targeted agent in first-line settings compared to gefitinib in patients with EGFR-mutated advanced NSCLC. Investigators compared PFS HRs of erlotinib *vs.* gefitinib using indirect treatment comparison (ITC) assessment based on the OPTIMAL study and the IPASS study. A significant PFS difference (ITC HR, 0.33; 95%CI: 0.19-0.58, $P = 0.0001$) was observed. Furthermore, this statistically significant PFS difference was also observed when comparing OPTIMAL with WJTOG 3405 (ITC HR, 0.48; 95%CI: 0.24-0.97, $P = 0.0395$) or with NEJ 002 (ITC HR, 0.53; 95%CI: 0.30-0.90, $P = 0.0307$).

Paz-Ares *et al*^[35] identified congress reports and papers reporting PFS for EGFR-mutated NSCLC treated with chemotherapy, erlotinib or gefitinib (phase II / III trials/retrospective analyses) in a literature search and checked for duplication and reported the results at the 2012 Annual Meeting of the European Society of Medical Oncology (ESMO). Data were included from 20 chemotherapy studies ($n = 984$), 27 erlotinib studies ($n = 735$) and 56 gefitinib studies ($n = 1843$). Longer PFS was seen with both EGFR-TKIs compared with chemotherapy across treatment lines. Pooled median PFS of all lines of therapy for erlotinib and gefitinib was 12.4 mo (95%CI: 11.6-13.4 mo; $n = 735$) and 9.3 mo (95%CI: 8.9-9.8 mo; $n = 1843$) respectively. Furthermore, in the studies where 90% or more of patients received EGFR-TKIs in first-line settings (predominantly first-line), pooled median PFS for erlotinib and gefitinib was 12.0 mo (95%CI:

Table 5 First-generation epidermal growth factor receptor tyrosine kinase inhibitor plus chemotherapy for unselected patients with non-small cell lung cancer

Ref.	Treatment	Number of patients	Response rate	Median PFS (mo)	Median OS (mo)
INTACT-1 ^[37]	CDDP + GEM + placebo	363	47%	6	10.9
	CDDP + GEM + gefitinib ^a	365	51%	5.8	9.9
	CDDP + GEM + gefitinib ^b	365	50%	5.5	9.9
INTACT-2 ^[38]	CDDP + PTX + placebo	345	29%	5.0	9.9
	CDDP + PTX + gefitinib ^a	345	30%	5.3	9.8
	CDDP + PTX + gefitinib ^b	347	30%	4.6	8.7
TRIBUTE ^[39]	CDDP + PTX + placebo	540	19%	4.9	10.5
	CDDP + PTX + erlotinib	539	22%	5.1	10.6
TALENT ^[40]	CDDP + GEM + placebo	586	30%	5.6	10.1
	CDDP + GEM + erlotinib	586	32%	5.4	9.9

^aDose of gefitinib is 250 mg; ^bDose of gefitinib is 500 mg. EGFR-TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC: Non-small cell lung cancer; PFS: Progression-free survival; OS: Overall survival; CDDP: Cisplatin; GEM: Gemcitabine; PTX: Paclitaxel.

10.8-13.3 mo; $n = 354$) and 9.7 mo (95%CI: 9.0-10.5 mo; $n = 716$) respectively. In contrast, pooled PFS of all lines of therapy and predominantly first-line for chemotherapy was 5.6 mo (95%CI: 5.3-6.0 mo; $n = 984$) and 5.8 mo (95%CI: 5.5-6.2 mo; $n = 868$) respectively. The investigators concluded that patients with activated mutant EGFR derived a greater benefit from EGFR-TKIs than from conventional chemotherapy, especially when administered as a first-line treatment.

Retrospective analysis of AEs comparing gefitinib with erlotinib showed that erlotinib appeared to have higher toxicity than gefitinib at each approved dose^[36]. Among 142 patients with NSCLC, including 107 treated with gefitinib and 35 treated with erlotinib who were retrospectively reviewed, 70 patients had an activating EGFR mutation. In the study, a significantly higher rate of AEs, including rash, stomatitis, constipation and anorexia, was observed in the erlotinib group. This group also had a tendency to require a dose reduction due to AEs. Further comparison of the frequency of grade 2 AEs showed that rash was the main reason for a dose reduction in a significantly higher percentage of patients in the erlotinib group.

CHEMOTHERAPY PLUS FIRST-GENERATION EGFR-TKIS IN PATIENTS WITH MUTATED EGFR

An earlier large randomized phase III trial of chemotherapy plus first-generation EGFR-TKI in unselected chemotherapy-naïve patients with advanced NSCLC, including the INTACT-1 study (chemotherapy plus gefitinib)^[37], the INTACT-2 study (chemotherapy plus gefitinib)^[38], the TRIBUTE study (chemotherapy plus erlotinib)^[39] and the TALENT study (chemotherapy plus erlotinib)^[40], failed to show superiority to standard platinum doublet chemotherapy in terms of RR, PFS and OS (Table 5).

In the CALGB 30406 study, a randomized phase II trial comparing erlotinib plus chemotherapy (carboplatin plus paclitaxel) to erlotinib monotherapy in chemotherapy- and EGFR-TKI-naïve patients with advanced

NSCLC, activating EGFR mutations were detected in 40% (66 of 164) of the enrolled patients^[41,42]. The response rate, PFS and OS of erlotinib plus chemotherapy were: 70%, 14.1 mo and 31.3 mo; and 73%, 17.2 mo and 38.1 mo, respectively. Although statistical comparison between erlotinib monotherapy and erlotinib plus chemotherapy was not carried out in patients with mutated EGFR in this study, longer survival, including PFS and OS, was found in patients with mutated EGFR treated with erlotinib plus chemotherapy. The FASTACT-2 study, a randomized double-blind trial comparing chemotherapy to intercalated combination of chemotherapy (gemcitabine plus cisplatin or carboplatin) and erlotinib in untreated patients with advanced NSCLC, met its primary endpoint of PFS (median PFS 7.6 mo *vs* 6.0 mo, HR, 0.57; $P < 0.0001$)^[43]. Among patients with mutated EGFR, median PFS and median OS were significantly longer in patients treated with chemotherapy plus erlotinib (PFS: 16.8 mo *vs* 6.9 mo, HR, 0.25; 95%CI: 0.16-0.39, $P < 0.0001$; OS: 31.4 mo *vs* 20.6 mo, HR, 0.48; 95%CI: 0.27-0.84, $P = 0.0092$). In contrast, no significant difference in PFS and OS between patients treated with chemotherapy plus erlotinib and patients treated with chemotherapy plus placebo was noted in patients with wild-type EGFR. Serious AEs were observed in 34% of patients in the chemotherapy plus placebo group and 31% of patients in the chemotherapy plus erlotinib group. The number of adverse events that led to discontinuation of the therapy was not significantly different between the 2 groups.

No prospective studies of EGFR-TKI plus chemotherapy as a first-line treatment in patients with EGFR-mutated advanced NSCLC have been conducted. Indirect comparison of data available from the INTACT 1 and 2 studies, the TRIBUTE study and the TALENT study indicates that EGFR-TKIs plus chemotherapy were effective in reducing the risk of disease progression in patients harboring an activating EGFR mutation compared to chemotherapy alone (HR, 0.54; 95%CI: 0.30-0.95, $P = 0.049$)^[30]. In contrast, EGFR-TKIs plus chemotherapy were not more effective than EGFR-TKIs in reducing the risk of disease progression (HR, 1.42; 95%CI:

Table 6 Clinical trials of second-generation epidermal growth factor receptor tyrosine kinase inhibitors (afatinib, dacomitinib) against non-small cell lung cancer expressing activated mutant epidermal growth factor receptor

Ref.	Phase	Treatment	Number of patients	Response rate	PFS (mo)	OS (mo)
LUX-Lung 2 ^[46]	II	Afatinib	106 ^a	66%	15.0	32
LUX-Lung 3 ^[47]	III	CDDP + PEM	104	NE	6.9	NE
LUX-Lung 6 ^[48]	III	Afatinib	204	NE	13.6	NE
		CDDP+GEM	122	23%	5.6	NE
		Afatinib	242	67%	11.0	NE
Kris <i>et al</i> ^[51]	III	dacomitinib	46	74%	18.2	NE

^aOf the 129 patients enrolled in the study, 106 patients tested positive for activating epidermal growth factor receptor mutations, including the exon 19 deletion mutation and L858R. PFS: Progression-free survival; OS: Overall survival; CDDP: Cisplatin; PEM: Pemetrexed; GEM: Gemcitabine; NE: Not evaluated.

0.80-2.53, $P = 0.23$) in patients with mutated EGFR.

SECOND-GENERATION EGFR-TKIS

The second-generation EGFR-TKIs, including afatinib^[45] and dacomitinib^[45], are intended to improve efficacy of treatment in patients with activated mutant EGFR and to improve the outcome in patients who acquired resistance to first-generation EGFR-TKIs. Table 6 shows previous studies of second-generation EGFR-TKIs, including afatinib and dacomitinib, for patients with advanced NSCLC carrying activated mutant EGFR.

Afatinib is an irreversible pan-HER-TKI and binds to EGFR receptors carrying the T790M substitution, which is the mutation conferring resistance to first-generation EGFR-TKIs. The LUX-Lung 2 study was a multicenter phase II trial evaluating the efficacy of afatinib 40-50 mg daily as a first- or second-line treatment in patients with EGFR-mutated advanced NSCLC^[46]. Among 129 patients enrolled in the study, 23 patients tested positive for uncommon EGFR mutations and the other cases were positive for activating EGFR mutations, including the exon 19 deletion mutation and L858R. The response rate, median PFS and median OS in patients harboring an activating EGFR mutation were 66%, 15.0 mo and 32.0 mo respectively. The most severe AEs (grade 3-4) were diarrhea and skin-related events and approximately a quarter of patients who developed these AEs received 50 mg of afatinib as an initial dose. Nearly 70% (of the 99 patients who had an initial dose of 50 mg) had to have their dose reduced to 40 mg and more than a half of these patients needed a further dose reduction to 30 mg. In 30 patients with a starting dose of 40 mg, a dose reduction to 30 mg was needed in 11 (37%) patients.

The LUX-Lung 3 study was a randomized phase III trial comparing afatinib to standard platinum doublet chemotherapy as a first-line treatment in patients with advanced EGFR-mutated lung adenocarcinoma^[47]. In total, 345 patients harboring EGFR mutations were randomly assigned to treatment groups (230 to afatinib and 115 to chemotherapy) and an activating EGFR mutation such as the exon 19 deletion mutation and L858R was detected in 308 patients (204 in the afatinib group and 104 in the chemotherapy group). Median PFSs were 11.1 mo for

afatinib and 6.9 mo for chemotherapy (HR, 0.58; 95%CI: 0.43-0.78, $P < 0.001$) in the enrolled patients and 13.6 mo for afatinib and 6.9 mo for chemotherapy (HR, 0.47; 95%CI: 0.34-0.65, $P < 0.001$) in patients harboring an activating EGFR mutation. Compared to chemotherapy, afatinib significantly delayed deterioration of cancer-related symptoms, including cough and dyspnea (cough, HR, 0.60; $P = 0.007$; dyspnea, HR, 0.68; $P = 0.015$). The prevalence of AEs leading to discontinuation of the therapy was similar in both groups. The most frequent AEs were diarrhea (95%), rash or acne (89%), stomatitis or mucositis (72%), paronychia (57%) and dry skin (29%) in patients treated with afatinib. Afatinib controlled cough and dyspnea better than chemotherapy, whereas diarrhea, dysphagia and sore mouth were worse with afatinib. Global health status/QoL was also improved over time with afatinib compared to chemotherapy.

At the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO), Wu *et al*^[48] reported the results of LUX-Lung 6, a randomized phase III trial comparing afatinib to standard platinum doublet chemotherapy as a first-line treatment in Asian patients with advanced EGFR-mutated lung adenocarcinoma. There were 364 chemotherapy-naïve patients (242 treated with afatinib, 122 treated with cisplatin plus gemcitabine). Afatinib was administered daily at 40 mg. This study met its primary endpoint with significant longer median PFS compared to chemotherapy (13.7 mo *vs* 5.6 mo, HR, 0.26; $P < 0.0001$). The response rate was significantly higher in patients treated with afatinib (66.9% *vs* 23.0%, $P < 0.0001$). Severe AEs (grade 3-5) were noted in 36% of patients treated with afatinib. The most common AEs were rash/acne (14.6%), diarrhea (5.4%) and stomatitis/mucositis (5.4%) in patients treated with afatinib. AEs leading to discontinuation of treatment were reported in 5.9% of patients treated with afatinib and 39.8% of patients treated with chemotherapy. Patient-reported outcomes showed significantly better control of cancer-related dyspnea, cough and pain with afatinib.

Dacomitinib is an irreversible pan-HER inhibitor and binds irreversibly to the adenosine triphosphate domain of 3 kinase-active members of the HER family, including EGFR, HER2 and HER4. In preclinical studies, dacomitinib showed greater antitumor activity in first-

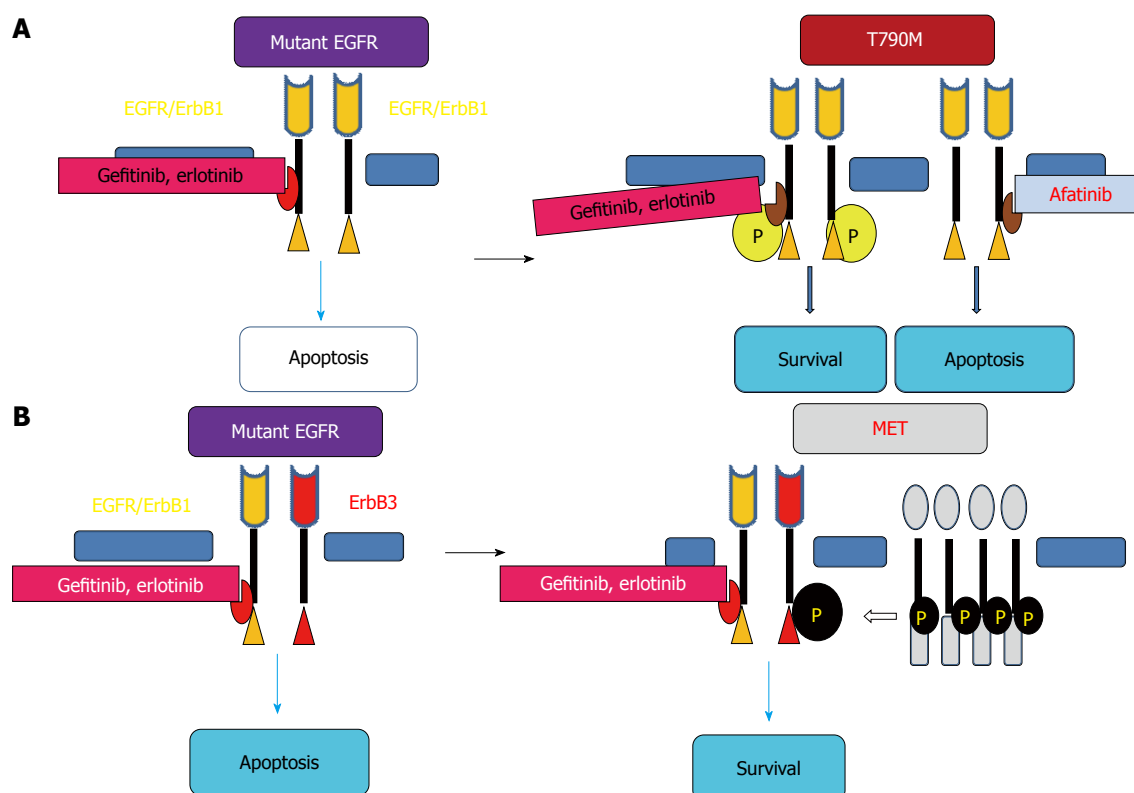


Figure 2 Major mechanisms of epidermal growth factor receptor resistance to epidermal growth factor receptor-tyrosine kinase inhibitors in lung cancer cell. Secondary epidermal growth factor receptor (EGFR) T790M mutation prevents binding of first-generation EGFR-tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib to EGFR, resulting in cancer cell survival (A). Afatinib inhibits the ATP-binding site of the tyrosine kinase associated with EGFR T790M, leading to apoptosis of cancer cell. MET amplification has been shown to confer resistance to EGFR-TKIs by activating phosphorylation of ErbB3 with activating of the PI3K/AKT pathway, resulting in cancer cell survival (B).

generation EGFR-TKI-resistant cell lines (including gefitinib and erlotinib) and in xenograft NSCLC models^[45,49]. In a randomized open-label trial comparing dacomitinib to erlotinib in previously treated patients with advanced NSCLC, 188 patients were randomly assigned to the 2 treatment groups^[50]. Although median PFS was significantly longer in patients treated with dacomitinib (2.9 mo *vs* 1.9 mo, HR, 0.66; 95%CI: 0.47-0.91, $P = 0.012$), no significant difference was noted in terms of median OS (9.5 mo *vs* 7.4 mo, HR, 0.80; 95%CI: 0.56-1.13, $P = 0.205$). Among all patients enrolled in the study, an activating EGFR mutation was detected in 30 patients (19 in the dacomitinib group, 11 in the erlotinib group). In patients with mutated EGFR, median PFS was 7.4 mo with either dacomitinib or erlotinib (HR, 0.46; 95%CI: 0.18-1.18, $P = 0.098$). AEs leading to treatment withdrawal were uncommon in both treatment arms. Common treatment-related adverse events were dermatological and gastrointestinal, predominantly grade 1 to 2, and more frequent with dacomitinib.

At the 2012 Annual Meeting of ASCO, Kris *et al.*^[51] reported the results of dacomitinib in chemotherapy-naïve patients with EGFR-mutated NSCLC. A total of 92 patients were enrolled in the study and 46 cases were positive for activating EGFR mutations. Among patients with mutated EGFR, RR was 74% (34 of 46 patients) and PFS at 4 mo after initiation of dacomitinib and PFS

were 95.5% (95%CI: 83.2-98.9%) and 18.2 mo (95%CI: 12.8-23.8 mo) respectively. For all 92 patients, common side effects (grade 3-4) were skin related toxicity (17%) and diarrhea (14%). Three patients (6.5%) with activated mutant EGFR discontinued the therapy because of drug-related toxicity.

TREATMENT AFTER A FAILURE OF FIRST-GENERATION EGFR-TKIS AGAINST EGFR-MUTATED NSCLC

Despite a good response and PFS benefits with first-generation EGFR-TKIs, the majority of responders ultimately develop resistance to the therapy after 9-14 mo^[7,9,11-12]. The most frequent secondary resistance to first-generation EGFR-TKIs is the EGFR T790M mutation (50%-60%) and the other mechanisms of resistance are amplification of the MET and HER2 genes, mutations in PIK3CA and BRAF, and conversion to small cell lung cancer^[52-54] (Figure 2). Approximately 30% of patients who acquired EGFR-TKI resistance have an unknown mechanism of resistance.

In the LUX-Lung 1 study, a randomized phase II b/III trial comparing afatinib to placebo in patients who failed first-generation EGFR-TKIs, 585 patients were randomly allocated to treatment groups (390 to afatinib

and 195 to placebo). Median overall survival was 10.8 mo (95%CI: 10.0-12.0 mo) in patients treated with afatinib and 12.0 mo (95%CI: 10.2-14.3 mo) in the placebo group (HR, 1.08; 95%CI: 0.86-1.35, $P = 0.74$). Median PFS was longer in the afatinib group than in the placebo group (3.3 mo *vs* 1.1 mo; $P < 0.0001$). The response rate was 7% (29 of 390 patients) in the afatinib group and 0.5% (1 of 195 patients) in the placebo group^[55].

Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively and with high affinity to the EGFR receptor^[56]. In a study of cetuximab in NSCLC patients previously treated with EGFR-TKIs, the response rate, median PFS and median OS were 0%, 1.8 mo (95%CI: 1.6-5.4 mo), 7.5 mo (95%CI: 2.2-19 mo) respectively. Among 3 patients who harbored an activating EGFR mutation, 1 maintained its stable disease effect for approximately 6 mo^[57].

Janjigian *et al*^[58] reported safety and efficacy results of a cohort study of the combination of afatinib and cetuximab in patients with NSCLC who had acquired resistance to erlotinib or gefitinib. One hundred patients were enrolled in the study and received the therapy. An activating EGFR mutation was detected in 94% (94/100) and the EGFR T790M mutation was detected in 53% (53/100) of the patients. Ninety-six patients were evaluated for efficacy of the therapy. Twenty-nine patients (30%) had PR to the therapy. Seventeen (32%) of 53 patients harboring the secondary-resistance EGFR T790M mutation had PR. Treatment-related toxicity leading to discontinuation of the therapy was observed in 19% of the patients. The most common AEs associated with the therapy were skin rash (97%) and diarrhea (71%).

LUX-Lung 4 was a phase II trial of afatinib in Asian patients who failed gefitinib or erlotinib or both^[59]. Of the 62 patients enrolled in the study, 45 patients had activating EGFR mutations. The response rate, median PFS and median OS were 8.2% (95%CI: 2.7-18.1%), 4.4 mo (95%CI: 2.8-4.6 mo), and 19.0 mo (95%CI: 14.9 mo to not achieved) respectively. Among 2 patients harboring an EGFR mutation who acquired the T790M mutation, 1 patient had stable disease for 9 mo and another for 1 mo. The most common treatment-related AEs were diarrhea (100%) and rash/acne (92%). Twenty-nine percent of the patients enrolled in the study discontinued the therapy due to afatinib-related AEs.

Several investigators have suggested that erlotinib may have a stronger biological activity than gefitinib based on their own findings. Gefitinib (250 mg per day) is typically administered at 1/3 of its maximum tolerated dose, whereas erlotinib (150 mg per day) is administered at its maximum tolerated dose. *In vitro* data showed that the mean concentration of gefitinib in blood plasma is 0.24 µg/mL at the 300 mg daily dose and 1.1 µg/mL at 1000 mg/d. In contrast, median concentration of erlotinib at 150 mg/d was 1.26 µg/mL. Previous findings suggest that erlotinib (150 mg/d) has a higher biological dose of EGFR inhibition than gefitinib (250 mg/d)^[60]. In the results of previous retrospective studies of second-line

erlotinib after a failure of gefitinib in patients harboring activating EGFR mutations, RR and PFS were 3%-10% and 2-3 mo respectively^[61-63]. The investigators suggested that subsequent erlotinib may elicit a response and a survival benefit in patients with mutated EGFR, with good performance status, good response and shorter duration of gefitinib administration (less than 12 mo).

DISCUSSION

Our recommended first- and second-line therapeutic regimens, mainly based on the results of phase III studies, are shown in Figure 3. First- and second-generation EGFR-TKIs, including gefitinib, erlotinib and afatinib, and cytotoxic chemotherapy are optimal first-line therapies in patients harboring activating EGFR mutations. Chemotherapy is recommended as a second-line treatment after failure of first-line EGFR-TKIs, including gefitinib, erlotinib and afatinib, and second-line therapy using these EGFR-TKIs is recommended in patients who failed chemotherapy. Subsequent erlotinib therapy may be a reasonable treatment in specific patients who failed first-line gefitinib therapy.

Although the data from several trials are insufficient to definitively determine the optimal treatment for EGFR-TKIs in patients with EGFR mutations, EGFR-TKIs play a key role in the treatment of patients harboring EGFR mutations and non-administration of these agents could adversely affect survival. Therefore, EGFR-TKIs should be administered early in the course of treatment, as a first- or second-line therapy, so that a chance to administer these agents is not missed due to clinical deterioration or severe toxicity after cytotoxic chemotherapy. Physicians should select either chemotherapy or an EGFR-TKI according to the patient's clinical condition, including PS, age, organ function and complications in non-elderly patients harboring an activating EGFR mutation. For elderly patients (75 years or older) who should not receive chemotherapy and/or patients with poor performance status (PS 3-4), first-line treatment with gefitinib may be considered.

No QoL assessment is currently available comparing second-line EGFR-TKIs after failure of chemotherapy to second-line chemotherapy after failure of EGFR-TKIs in patients harboring an activating EGFR mutation, which is problematic. Furthermore, it is unclear which EGFR-TKI(s) are most desirable as an initial therapy and whether second-generation EGFR-TKIs can overcome acquired secondary resistance to first-generation EGFR-TKIs in NSCLC. Additionally, the appropriate timing for discontinuation of EGFR-TKIs after confirmation of tumor progression is not clear. Some retrospective studies suggest that continuation of EGFR-TKIs beyond disease progression may prolong overall survival of patients with mutated EGFR, with a good therapeutic response^[64,65]. Investigators concluded that EGFR-TKI responders should continue the therapy until the clinical condition and/or imaging findings are reversed to the condition at therapy initiation. Treatment assessment based on

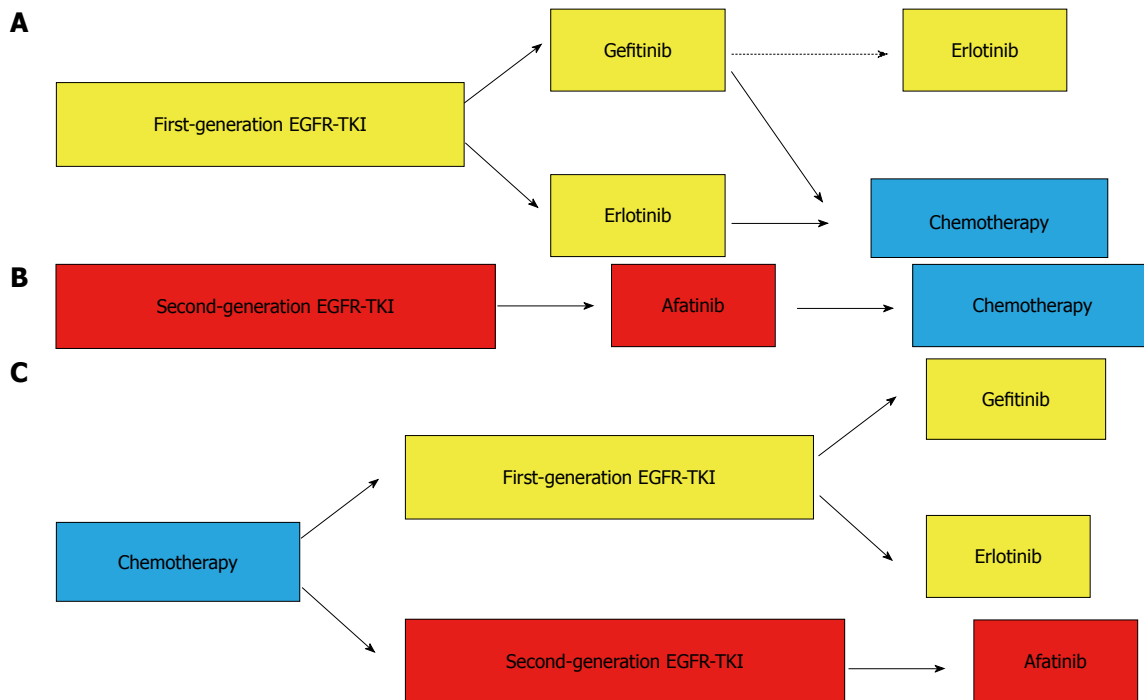


Figure 3 First- and second-line treatment strategies for activating epidermal growth factor receptor-mutated advanced non-small cell lung cancer. First- or second-generation EGFR-tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib and afatinib, are recommended as initial EGFR-TKI therapy (A and B). First-line gefitinib is recommended in patients with poorer performance status who cannot be treated with systemic chemotherapy. First- (C) or second-line (A and B) cytotoxic chemotherapy is recommended in chemotherapy naïve patients. Subsequent erlotinib may be useful in specific patients who failed gefitinib (A).

Table 7 Ongoing trials for advanced activating epidermal growth factor receptor -mutated non-small cell lung cancer

Line	Trial	Phase	Treatment	Primary endpoint
First	LUX-Lung 7 (NCT01466660)	II b	Afatinib <i>vs</i> Gefitinib	PFS/OS
	ARCHER-1050 (NCT01774721)	III	Dacomitinib <i>vs</i> Gefitinib	PFS
	Tamiya <i>et al</i> ^[65] (UMIN000005503)	II	CBDCA + TS-1 + gefitinib	PFS
	NEJ 009 (UMIN000006340)	III	CBDCA + PEM + gefitinib <i>vs</i> Gefitinib	OS
Second/third	WJOG (UMIN000002014)	III	Gefitinib <i>vs</i> Erlotinib	PFS
	IMPRESS (NCT01544179)	III	Continuation of gefitinib + CDDP + PEM <i>vs</i> CDDP+PEM	PFS
	JMTO12-01 (UMIN000007765)	II	Continuation of gefitinib + DOC/PEM <i>vs</i> DOC/PEM	PFS

EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; PFS: Progression-free survival; OS: Overall survival; CBDCA: Carboplatin; PEM: Pemetrexed; CDDP: Cisplatin; DOC: Docetaxel.

response evaluation criteria in solid tumors (RECIST) may be unsuitable for EGFR-TKIs and a new treatment assessment that may impact survival is needed^[66]. Table 7 shows the ongoing trials for patients harboring activating EGFR mutations. The results of these studies will provide considerable information for EGFR-TKI selection for EGFR-mutated NSCLC. In the future, investigators need to assess the QoL of patients treated with EGFR-TKIs and to compare first- and second-line administration in the same study population.

CONCLUSION

In summary, the data reported suggest that activating EGFR mutations may play a key role in the efficacy of EGFR-TKIs. Administration of first- and second-generation EGFR-TKIs as first- or second-line therapy is an optimal strategy in patients with EGFR-mutated

advanced NSCLC. Second-generation EGFR-TKIs may be superior to first-generation EGFR-TKIs because of their stronger biological activity. Ongoing trials of EGFR-TKIs may identify an EGFR-TKI that is most applicable as an initial EGFR-TKI treatment. Furthermore, the results of these trials may establish new treatment guidelines for activating EGFR-mutated NSCLC and for NSCLC with acquired secondary resistance.

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