

First-line Use of EGFR Tyrosine Kinase Inhibitors in Patients With NSCLC Containing EGFR Mutations

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Abstract: While the small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib have modest clinical benefit in unselected patients with non-small cell lung cancer after platinum-based chemotherapy, an emerging and potentially more elegant strategy is to move these agents to the frontline setting for select patients. Those with somatic mutations in EGFR respond dramatically to EGFR inhibitors, and mounting evidence from recent clinical trials, particularly the Iressa Pan-Asia Study (IPASS) trial, confirms superior response rates, progression-free survival, and tolerability with this targeted therapy compared with conventional chemotherapy. Here, we review the studies supporting the use of EGFR tyrosine kinase inhibitors in the frontline setting in patients with EGFR mutations.

Introduction

Despite recent advances in imaging and treatment, lung cancer remains responsible for the highest cancer-related mortality in the United States.¹ Worldwide, the increasing prevalence of smoking in developing nations foreshadows a growing public health epidemic in the coming decades. Non-small cell lung cancer (NSCLC) comprises 85% of lung cancers.² Research into the molecular pathogenesis of NSCLC has unveiled a critical role for the epidermal growth factor receptor (EGFR) signaling pathway. Initially tested broadly in patients with NSCLC, it has become clear that the EGFR small molecule tyrosine kinase inhibitors (TKIs) gefitinib (Tarceva, Genentech/OSI Pharmaceuticals) and erlotinib (Iressa, AstraZeneca) particularly affect NSCLC tumors with EGFR mutations, but only modestly affect most wild-type tumors. This article will review the historical use of gefitinib and erlotinib in unselected patients, the association between the presence of EGFR mutations and response to TKI, and the mounting clinical evidence supporting frontline therapy with TKIs in selected patients with advanced NSCLC and EGFR mutations.

Keywords

NSCLC, tyrosine kinase inhibitors, epidermal growth factor receptor, erlotinib, gefitinib

EGFR Inhibitors in Unselected Patients With NSCLC

EGFR (ErbB-1) is the prototypical transmembrane receptor tyrosine kinase in the ErbB signaling pathway, which also includes human epidermal growth factor receptor 2 (HER-2/Neu, ErbB-2), ErbB-3, and ErbB-4.³ Ligand binding to EGFR leads to receptor dimerization, activation of the intracellular tyrosine kinase domain, and formation of phosphorylated protein docking targets, which transduce intracellular signals via the MAP-kinase, PI3-kinase, and STAT networks. The resulting gene transcription programs promote cellular growth and inhibit apoptosis. The EGFR signaling pathway is often aberrantly activated in NSCLC via increased protein expression, gene copy number, or mutations in the tyrosine kinase domain, leading to constitutive activation and tumorigenesis.^{4,5}

Following the success of the TKI imatinib (Gleevec, Novartis) in the treatment of chronic myelogenous leukemia,^{6,7} EGFR seemed poised as a similar candidate for targeted therapy in NSCLC. Two orally administered small molecules, gefitinib and erlotinib, were developed; they potently inhibited the EGFR tyrosine kinase by blocking the adenosine triphosphate binding pocket.⁸⁻¹² Phase I trials confirmed activity in patients with advanced, refractory NSCLC.¹³⁻¹⁶ Dose-limiting toxicities of acneiform rash and diarrhea were observed at doses above 700 mg/day of gefitinib, but EGFR appears to be inhibited in skin biopsies at doses as low as 150 mg daily,¹⁷ therefore 250- and 500-mg/day doses were selected for further study. Erlotinib was found to have a virtually identical toxicity profile but a higher potency, thus the maximum tolerated dose (MTD) of 150 mg/day was brought forward for subsequent studies.

In parallel, both drugs advanced through phase II testing. For gefitinib, 2 large phase II trials, IDEAL-1 and IDEAL-2, randomized 430 patients with refractory NSCLC who had previously received platinum-based chemotherapy to 2 different dose levels of gefitinib.^{18,19} The trials demonstrated single-agent response rates of approximately 10–20% and median survival times of 6–8 months. Based on these results, gefitinib received approval from the U.S. Food and Drug Administration (FDA) for the orphan indication of third-line treatment of NSCLC in 2003. Both the 250 mg and 500 mg doses were similarly effective, but the 250 mg dose was more tolerable and became the approved dose. Erlotinib was studied in a smaller single-arm phase II trial of 57 patients with refractory advanced NSCLC.²⁰ Similarly to the IDEAL trials, a response rate of 12% and median survival of 8.4 months were reported.

Combination platinum-based chemotherapy improves survival by 3 months or more compared to best supportive care for patients with advanced NSCLC, and a comparison of different chemotherapy regimens by Schiller and colleagues demonstrated equivalence of multiple common regimens.^{21,22} In order to improve upon the doublet chemotherapy platform for NSCLC, these targeted drugs were next tested in the frontline setting in 4 large, randomized, phase III trials that added gefitinib or erlotinib to cisplatin/gemcitabine or carboplatin/paclitaxel chemotherapy backbones (known as INTACT-1, INTACT-2, TRIBUTE, and TALENT).²³⁻²⁶ For unclear reasons, all 4 trials failed to demonstrate either an improved response or a survival benefit from the combination of a TKI with chemotherapy (Table 1). Based on these trials, the simultaneous first-line administration of gefitinib or erlotinib and chemotherapy to unselected patients appears ineffective, but phase II studies are currently exploring alternative regimens of chemotherapy and TKIs in an attempt to separate interference of potential cytostatic and cytotoxic effects of each agent.²⁷

Despite the failure of the first-line trials, 2 additional phase III trials were completed to confirm the previously observed activity in refractory NSCLC. For the first time, these trials described divergent results between gefitinib and erlotinib. The BR.21 trial randomized patients previously treated with chemotherapy to erlotinib or placebo, and showed a significant improvement in response rate (9% vs 1%) and overall survival (OS; 6.7 vs 4.7 months; $P < .001$) with erlotinib.²⁸ However, the similar ISEL trial examining gefitinib or placebo failed to demonstrate a survival difference (5.6 vs 5.1 months; $P = \text{NS}$; Table 1).²⁹ Hence, in 2004, the FDA approved erlotinib for second- and third-line treatment of NSCLC, but the approved use of gefitinib was restricted to patients who previously had received clinical benefit or patients in clinical trials. However, gefitinib continued to be used in Asia and in clinical trials in the United States. Potential reasons for the observed difference between the trials include the difference in the doses of each drug relative to its MTD, the inclusion of a more treatment-refractory population in ISEL, and undocumented variation in the study populations with regard to EGFR mutation status.

Subsequently, a number of trials have confirmed the modest benefit of erlotinib in unselected patients with NSCLC, and also demonstrated a survival benefit of gefitinib in the second-line setting, outlined in Table 1. The SATURN study randomized 889 patients with response or stable disease after 4 cycles of platinum-based doublet chemotherapy to “switch maintenance” therapy with erlotinib or placebo. Cappuzzo and coworkers have reported preliminary data that showed an improvement

Table 1. Large Studies Using Gefitinib or Erlotinib in Unselected Patients With Advanced Non-small Cell Lung Cancer

Study	Population	Treatment Arms	Number of Patients	Response Rate (%)	Median Survival (months)	
INTACT-1 ²³	First-line	Cisplatin/gemcitabine/gefitinib 500 mg/day	365	50	9.9	
		Cisplatin/gemcitabine/gefitinib 250 mg/day	365	51	9.9	
		Cisplatin/gemcitabine/placebo	363	47	10.9	
INTACT-2 ²⁴	First-line	Carboplatin/paclitaxel/gefitinib 500 mg/day	347	30	8.7	
		Carboplatin/paclitaxel/gefitinib 250 mg/day	345	30	9.8	
		Carboplatin/paclitaxel/placebo	345	29	9.9	
TALENT ²⁶	First-line	Cisplatin/gemcitabine/erlotinib 150 mg/day	533	32	9.9	
		Cisplatin/gemcitabine/placebo	536	30	10.1	
TRIBUTE ²⁵	First-line	Carboplatin/paclitaxel/erlotinib 150 mg/day	539	22	10.6	
		Carboplatin/paclitaxel/placebo	540	20	10.5	
ISEL ²⁹	Prior platinum-based	Gefitinib 250 mg/day	1129	8*	5.6	
		Placebo	563	1*	5.1	
BR.21 ²⁸	Prior platinum-based	Erlotinib 150 mg/day	488	9*	6.7*	
		Placebo	243	1*	4.7*	
INTEREST ³³	Prior platinum-based	Gefitinib 250 mg/day	723	9	7.6 [†]	
		Docetaxel	710	8	8.0 [†]	
SATURN ³⁰	First-line	Platinum-based doublet, then:	Erlotinib 150 mg/day	438	12*	12.0*
			Placebo	451	5*	11.0*
ATLAS ³²	First-line	Platinum-based doublet + bevacizumab, with nonprogressive disease	Bevacizumab + erlotinib 150 mg/day	373	NA	4.8 [‡]
			Bevacizumab + placebo	370	NA	3.8 [‡]

*Significant difference between groups.

[†]Noninferiority established between groups.

[‡]Progression-free survival; significant difference between groups.

NA=not reported or unavailable.

in OS from 11 to 12 months (hazard ratio [HR], 0.81; $P=.0088$), favoring early erlotinib.³⁰ The ongoing ATLAS trial uses a similar design but includes the use of bevacizumab (Avastin, Genentech) in both treatment arms, based on the previous phase III trial demonstrating that bevacizumab improves OS in combination with carboplatin and paclitaxel.³¹ In ATLAS, 743 patients who received platinum-based chemotherapy with bevacizumab were randomized to maintenance bevacizumab alone or bevacizumab plus erlotinib.³² This study met its primary

endpoint and demonstrated an improved median progression-free survival (PFS) from 3.8 to 4.8 months (HR, 0.72; $P=.0012$), but OS data are not yet available. Finally, the phase III INTEREST trial tested the noninferiority of gefitinib compared with docetaxel as second-line therapy, and demonstrated in 1,466 randomized patients that median OS in patients treated with gefitinib (7.6 months) was not worse than in patients treated with docetaxel (8.0 months),³³ which previously had been compared with best supportive care in advanced NSCLC.³⁴ Taken

together, these studies suggest a modest but significant benefit for EGFR TKI therapy in the second-line treatment of unselected patients with NSCLC. However, the repeated observation that a subpopulation of patients from many of these studies experienced dramatic tumor responses to EGFR TKIs suggested that clinical or molecular features might be able to help select patients who would benefit most from therapy.

Clinical Characteristics of TKI-response and EGFR Mutations as a Biomarker

While second-line EGFR TKI monotherapy appears to improve survival in unselected patients with NSCLC, retrospective subgroup analysis of many of the clinical trials mentioned above revealed that patients with particular clinical features were more likely to benefit from therapy. Such patients included those with tumors of adenocarcinoma histology, women, Asians, and those who were light or never smokers.^{28,29} Even in the overall negative TRIBUTE study, the never-smoker subset of patients had a higher response rate and a doubling in median OS after treatment with erlotinib compared to patients who previously had smoked.²⁵

DNA sequencing of tumors from multiple series of patients with dramatic responses to gefitinib, compared with patients without responses, revealed the presence of characteristic genetic mutations in the EGFR gene.³⁵⁻³⁷ The previously identified clinical markers of response to EGFR TKIs were found to be commonly associated with the presence of these mutations; thus, these clinical features are actually believed to be surrogates for the molecular biomarker of EGFR mutation. The strong connection between response to EGFR TKIs and the presence of EGFR mutations was affirmed in a recent systematic review of 59 studies using first-line TKI treatment that included responses stratified by EGFR mutation status. This meta-analysis demonstrated that EGFR mutations predict response to EGFR TKIs, with a sensitivity of 0.78 (95% confidence interval [CI], 0.74–0.82).³⁸ Many individual studies have also demonstrated better PFS and OS in patients with EGFR mutations that are treated with an EGFR TKI than in patients without such a mutation, suggesting that response to TKI treatment may also correspond to an improvement in survival.³⁹⁻⁴⁴

Over 90% of EGFR tyrosine kinase domain mutations associated with sensitivity to EGFR TKI therapy fall into 2 categories: in-frame deletions in exon 19 and the L858R point mutation in exon 21, as reviewed by Sharma and colleagues.⁴⁵ These mutations appear to specifically activate both cell proliferation and survival signals.⁴⁶ Therefore, tumors with EGFR mutations are “oncogene addicted” to EGFR survival signals, relying exclusively

upon the EGFR signaling cascade to maintain viability, which explains their exquisite sensitivity to TKI therapy.

In contrast to the presence of EGFR mutations, the putative biomarkers of EGFR protein expression and elevated gene copy number have not consistently proven to be robust molecular predictors of response to TKIs. Though EGFR protein expression, as measured by immunohistochemistry, does not appear to correlate with response,^{47,48} the significance of elevated EGFR gene copy number has been the subject of significantly more controversy. Multiple early studies demonstrated a relationship between elevated EGFR gene copy number, as detected by quantitative polymerase chain reaction or fluorescence in situ hybridization (FISH),^{40,44,49,50} whereas more recent studies have shown either no association or even an inverse association between elevated gene copy number and response to TKIs.^{33,51-53} The ONCOBELL trial was initiated to enrich for this population by treating patients who had never smoked or were FISH- or phospho-Akt positive with second-line gefitinib, and demonstrated a response rate of 48% and PFS of 6.4 months.⁵⁴ This study reported an association between treatment effect and FISH-positive tumors, but many of the FISH-positive patients also had EGFR mutations. Because some tumors may have both EGFR mutations and increased EGFR gene copy number, the predictive value of FISH may be mostly attributed to the association between these 2 genetic events.

Selection of Patients for First-line TKI Therapy

Given the molecular biology of EGFR-mutant NSCLC, its particular sensitivity to TKIs, and the improved toxicity profile of TKIs compared to standard chemotherapy, a number of recent trials have attempted to enrich for patients more likely to benefit from first-line TKI treatment. Some have used EGFR mutations to identify patients, whereas others have used clinical criteria associated with response to TKIs, such as histology, smoking status, sex, and ethnicity; others have selected patients with potential intolerance to chemotherapy based on performance status and age. As described below, EGFR mutation status has emerged as the most important factor predictive of benefit to first-line EGFR TKI therapy.

Trials using a purely clinical selection of patients who would be expected to be intolerant to chemotherapy have not demonstrated superiority of TKIs over standard care. A randomized trial by Goss and associates compared gefitinib with supportive care in patients with poor performance status and showed no difference in survival or response rate.⁵⁵ In the INVITE trial, 198 patients over the age of 70 were randomized to gefitinib versus single-agent

Table 2. Studies Using First-line Gefitinib or Erlotinib in Selected Patients With Advanced Non-small Cell Lung Cancer

Study	Location	Selection	Treatment	Patients	Response Rate	Median PFS (mo)	Median OS (mo)
Goss ⁵⁵	Canada	Unfit for chemotherapy	Gefitinib	100	6%	1.4	3.1
			Placebo	101	1%	1.3	2.7
INVITE ⁵²	Italy	Over age 70	Gefitinib	97	3%	2.7	6.4
			Vinorelbine	99	5%	2.9	6.2
Miller ⁵¹	USA	BAC histology (Note: 25% had prior chemotherapy)	Erlotinib	101	22%	4	17
			Subset: EGFR mutation positive	18	83%	13	23
SWOG 0126 ⁶⁷	USA	BAC	Gefitinib, 500 mg/day	69 (previously untreated)	17%	4	13
Asahina ⁵⁶	Japan	Mutation positive	Gefitinib	16	75%	8.9	NR
Inoue ⁵⁸	Japan	Mutation positive	Gefitinib	25	75%	9.7	NA
van Zandwijk ⁵⁹	The Netherlands	Mutation positive	Gefitinib or erlotinib	13	85%	NA	NA
Yoshida ⁵⁷	Japan	Mutation positive	Gefitinib	21	90%	7.7	NR
Sequist ⁶⁰	USA	Mutation positive	Gefitinib	31	55%	9.2	NA
Inoue ⁶¹	Japan	Mutation positive, unfit for chemotherapy	Gefitinib	30	66%	6.5	17.8
Rosell ⁶²	Spain	Mutation positive	Erlotinib	350	70%	14.0	27.0
IPASS ⁶⁴	Asia	Light smoker, adenocarcinoma	Gefitinib	609	43%	5.7	NA
			Chemotherapy	608	32%	5.8	NA
		Subgroup: Mutation positive	Gefitinib	132	71%	9.6	NA
			Chemotherapy	103	47%	6.3	NA
		Subgroup: Mutation negative	Gefitinib	91	1%	1.6	NA
			Chemotherapy	85	24%	5.5	NA
Kobayashi ⁶⁵	Japan	Mutation positive	Gefitinib	98	74%	10.4	NA
			Carboplatin/paclitaxel	99	29%	5.5	NA
Mitsudomi ⁶⁶	Japan	Mutation positive	Gefitinib	88	62%	9.2	NA
			Cisplatin/docetaxel	89	32%	6.3	NA

BAC=bronchioloalveolar carcinoma; EGFR=epidermal growth factor receptor; NA=not available; NR=not reached; OS=overall survival; PFS=progression-free survival.

vinorelbine. Gefitinib was better tolerated, but showed equivalent efficacy.⁵² Therefore, gefitinib may have a limited role in the treatment of patients otherwise unable to tolerate chemotherapy, but prospective selection by molecular criteria is potentially a more powerful tool for identifying patients likely to benefit, as discussed below.

A number of phase II trials have selected patients with EGFR mutations for first-line treatment, all of which demonstrated impressive response rates of over 50% and time to progression of approximately 9 months (Table 2).⁵⁶⁻⁵⁹ A study from our group, the first such trial in Western patients, supports the concept that patients

with EGFR mutations treated with first-line gefitinib respond dramatically to treatment⁶⁰; even poor performance status and elderly patients with mutations appear to benefit. A single-arm trial that selected patients with EGFR mutations and performance status of 3–4 or elderly age demonstrated a 66% response rate, a PFS of 6 months, and an OS of 18 months following first-line TKI therapy, which far exceeds historical expectations for poor chemotherapy candidates.⁶¹ Erlotinib has at least the same magnitude of benefit in patients with mutations. In a recent, large study by Rosell and associates, 350 patients from Spain with EGFR mutations were treated with first-line erlotinib. The observed response rate was 70%, with a PFS of 14 months and an OS of 27 months, more than double that expected from chemotherapy.⁶²

However, these single-arm studies leave a few outstanding questions. First, is clinical selection of patients a viable substitute for EGFR mutations? Also, do patients with EGFR mutations benefit more from first-line TKI treatment than from chemotherapy? Since it has been observed that patients with EGFR mutations have a better overall prognosis than unselected patients with NSCLC even in the absence of TKI treatment, it has been proposed that the excellent response rates and survival in the phase II studies of patients with mutations may be simply due to a slower course of the disease for these patients.⁶³

The recent IPASS study from Asia suggests that clinical selection of patients alone is inadequate and establishes a rationale for first-line TKI treatment of patients with EGFR mutations.⁶⁴ In this study, 1,217 never-smoking or formerly light-smoking Asian patients with NSCLC of adenocarcinoma histology were randomized to receive gefitinib or carboplatin and paclitaxel chemotherapy. Within this clinically selected group of patients, the trial demonstrated that gefitinib treatment was superior to chemotherapy for PFS (HR, 0.74; 95% CI, 0.65–0.85; $P < .001$). In addition, patients that received gefitinib had fewer treatment-related side effects and an improved quality of life.

EGFR mutation testing was performed on 437 available tumor samples. In a preplanned subgroup analysis, 261 patients with EGFR-mutation positive tumors had a response rate of 71%, whereas 176 patients without a mutation had a response rate of only 1%. Similarly, the HR for PFS was 0.48 (95% CI, 0.36–0.64), favoring gefitinib in the mutation-positive cohort with a median PFS of 9.6 months for gefitinib versus 6.3 months for chemotherapy. Notably, in the EGFR wild-type group, first-line gefitinib was harmful, with an HR of 2.85, reinforcing the concept that clinical characteristics alone are not sufficient to make first-line therapy decisions, and molecular information is required. Though OS data are

eagerly awaited, they may not ultimately differ, due to an equal 30% treatment crossover rate in both arms. Of the patients with EGFR mutations, the 3-month longer PFS and higher response rate, in addition to the improved quality of life, suggest that first-line TKI treatment should be strongly considered in all patients with known EGFR mutations. In contrast, TKI treatment should be used with caution in patients with unknown mutation status, since clinical selection criteria alone are insufficient to predict response to TKIs.

One criticism of the IPASS study is that it used retrospective EGFR mutation testing, and samples were available from only 30% of enrolled patients. However, a similar study performed by the North East Japan Study Group, preliminarily reported at the 2009 meeting of the American Society of Clinical Oncology, prospectively tested patients for EGFR mutations and randomized 194 to gefitinib versus chemotherapy.⁶⁵ PFS was significantly better in the gefitinib group (10.4 vs 5.5 months, HR, 0.36; 95% CI, 0.25–0.51). A second confirmatory study from the West Japan study group randomized 172 patients with EGFR mutations to first-line gefitinib or cisplatin and docetaxel, and demonstrated significantly better PFS of 9.2 versus 6.3 months (HR, 0.489; 95% CI, 0.336–0.710; $P < .0001$).⁶⁶ These studies consistently show a significant PFS advantage to initial TKI therapy instead of chemotherapy in patients with known EGFR mutations.

Conclusions

The small molecule EGFR inhibitors erlotinib and gefitinib were first shown to be effective in second- and third-line treatment of NSCLC, but did not appear to be effective in combination with chemotherapy in the first-line setting. The identification of somatic mutations in the EGFR gene in some patients with NSCLC, as well as the realization that these patients are particularly sensitive to EGFR inhibition, has led to the investigation of these agents in the first-line setting in patients with EGFR mutations. Recent randomized trials reinforce the concept that patients with EGFR mutations treated initially with TKIs have improved response rates, longer PFS, and fewer symptoms than those treated with chemotherapy.

Presently, EGFR mutation testing is commercially available with an estimated turnaround time of 8–10 days, but the resulting treatment delay may be a deterrent to first-line treatment with EGFR TKI therapy for some patients. The IPASS results also caution us that if EGFR mutation results are not available and urgent treatment is required, chemotherapy should be given regardless of whether the genotype has been confirmed. As technology improves to allow more rapid identification of mutations

in fragments of fixed tumor tissue, perhaps by transitioning from sequencing-based analysis to “hotspot” allele-specific testing with a turnaround time of less than 1 week, we anticipate that patients with EGFR mutations will increasingly be offered first-line TKI therapy.

With the widespread availability of EGFR TKIs and their continued activity in the second-line setting,⁶² a survival advantage may be impossible to demonstrate with the design of current randomized trials. However, EGFR TKI therapy is the most active treatment for these patients. The superior 70% response rate and better PFS of over 9 months, combined with a better quality of life as observed in the IPASS trial, demonstrates that first-line TKI therapy is better tolerated with a longer duration of benefit than chemotherapy. Therefore, we would strongly consider first-line EGFR TKI therapy in patients with EGFR mutations, even if the first-line trials of EGFR TKIs in patients with mutations ultimately fail to show a survival advantage when mature analyses are available. In the future, we hope that continued development of targeted therapies such as EGFR TKIs will bring us closer to the ultimate goal of long-term disease control or even a cure for patients with advanced lung cancer.

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