Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians

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Abstract: Inhibition of epidermal growth factor receptor (EGFR) has become an important target in the treatment of advanced non-small cell lung cancer (NSCLC). Erlotinib and gefitinib, two small molecular agents that target the tyrosine kinase domain of the EGFR, were approved in many countries for the treatment of locally advanced or metastatic NSCLC as a second- or third-line regimen. Since then, randomized trials have evaluated the role of these two targeted agents alone or combined with chemotherapy in maintenance and first-line settings. This review summarizes the results of recent clinical trials with these tyrosine kinase inhibitors, with a focus on erlotinib, as first-line treatment towards a form of personalized medicine aimed at improving clinical outcome in advanced NSCLC.

Keywords: clinical trials, erlotinib, first-line, non-small cell lung cancer, treatment

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [Jemal *et al*. 2009]. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers and approximately half of the patients present with advanced disease at the time of diagnosis [Yang *et al*. 2005]. Most patients will, therefore, face the option of palliative chemotherapy [Rinaldi *et al*. 2006]. Unfortunately, the improvement in overall survival (OS) with platinum-based doublets is modest although statistically significant when compared with the best supportive care [Schiller *et al*. 2002]. Despite the fact that platinum-based chemotherapy can control cancer-related symptoms and improve survival, there is still an urgent need for developing new agents.

The availability of targeted agents has become an invaluable resource in the treatment of advanced NSCLC. The epidermal growth factor receptor (EGFR) plays an important role in the development and progression of NSCLC [Normanno *et al*. 2003]. In recent years the two small molecules, erlotinib and gefitinib, have been developed and extensively studied in patients with NSCLC. Both drugs are orally available small molecules that selectively and reversibly inhibit the tyrosine kinase domain of EGFR. Phase I clinical trials demonstrated their antitumor activity in NSCLC [Hidalgo *et al*. 2001; Siu *et al*. 1999; Pollack *et al*. 1999; Herbst *et al*. 2002; Baselga *et al*. 2002]. Furthermore, BR.21, a large randomized placebo-controlled phase III trial [Shepherd *et al*. 2005] showed that erlotinib was superior to placebo in terms of overall survival (OS; 6.7 months *versus* 4.7 months, respectively) and symptoms control. Thus, it has been incorporated into treatment algorithms for patients progressing after standard chemotherapy. However, proper selection of patients appears to be crucial with targeted agents. In 2004, distinct study groups found that EGFR mutation status emerged as an important predictor of response to or survival benefit of EGFR tyrosine kinase inhibitors (TKIs) [Paez *et al*. 2004; Lynch *et al*. 2004]. In this article, we summarize current data of clinical trials with EGFR TKIs, especially erlotinib, for advanced NSCLC and discuss its impact on treatment algorithms in advanced NSCLC.

Erlotinib or gefitinib *versus* placebo in second- and third-line treatment of NSCLC

A number of phase III clinical trials have demonstrated the efficacy of EGFR TKIs on NSCLC. Shepherd and colleagues performed a double-blind, phase III clinical trial where 731 patients

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Table 1. Erlotinib or gefitinib *versus* placebo in second- or third-line settings.

Trial	Study phase	Treatment	Number of patients	ORR (%)	Median PFS/ TTP (months)	Median OS (months)
BR.21 [Shepherd *et al*. 2005]	Phase III	Erlotinib	$N = 488$	8.9	2.2	6.7
		Placebo	$N = 243$	<1	1.8	4.7
				$p < 0.001$	$p < 0.001$	$p < 0.001$
ISEL [Thatcher *et al*. 2005]	Phase III	Gefitinib	$N = 1129$	8	3.0	5.6
		Placebo	$N = 563$	1.3	2.6	5.1
				$p < 0.0001$	$p = 0.0006$	$p = 0.089$

ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival

were randomized to either erlotinib or placebo after failure of first-line or second-line chemotherapy [Shepherd *et al*. 2005]. The response rate was 8.9% in the erlotinib group and <1% in the placebo group ($p < 0.001$). The median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival (PFS) was 2.2 months and 1.8 months, respectively (hazard ratio [HR] 0.61, $p < 0.001$). OS was 6.7 months and 4.7 months, respectively (HR 0.70; $p < 0.001$) in favor of erlotinib (Table 1). The subgroup analysis showed that the likelihood of a response to erlotinib was higher among women ($p = 0.006$), nonsmokers ($p < 0.001$), Asians ($p = 0.02$), and patients with adenocarcinoma ($p < 0.001$). Cox regression analysis showed that erlotinib remained associated with longer survival ($p = 0.002$) among patients of Asian origin ($p = 0.01$), those with adenocarcinoma on histologic examination ($p = 0.004$), and those never having smoked ($p = 0.048$ *versus* current or past smoking). Erlotinib was associated with a higher incidence of toxicity compared with placebo: the most common toxicities included rash (12%) and diarrhea (5%); however, most toxicities were manageable. Erlotinib also improved symptoms control and quality of life.

The phase III Iressa Survival Evaluation in Lung Cancer (ISEL) trial compared gefitinib with placebo (2:1) in 1692 patients with refractory advanced NSCLC [Thatcher *et al*. 2005]. At median follow up of 7.2 months, median survival did not differ significantly between the groups in the overall population (5.6 months for gefitinib and 5.1 months for placebo; HR 0.89, 95% confidence interval [CI] 0.77–1.02, $p = 0.087$; Table 1). However, subgroup analyses showed significantly longer survival in the gefitinib group than in the placebo group for never smokers ($n = 375$; median survival 8.9 *versus* 6.1 months; HR 0.67, 95% CI 0.49–0.92, $p = 0.012$), and in patients of Asian origin ($n = 342$; median survival 9.5 *versus* 5.5 months; HR 0.66, CI 0.48–0.91, $p = 0.01$). The most common adverse events (AEs) in the gefitinib group were rash and diarrhea. As in previous studies, gefitinib was well tolerated.

Comparison between studies showed that gefitinib and erlotinib produced similar response rates (8% *versus* 9%). However, erlotinib demonstrated the survival benefit for all enrolled subjects, while gefitinib only showed survival benefit for patients with adenocarcinoma or never smokers. The two studies were of similar design but the main difference between the patient groups was previous response to treatment: in the ISEL trial, 45% of the patients in the gefitinib group had progressed and 18% had responded to their most recent chemotherapy regimen whereas 28% of patients in the erlotinib group had progressed and 38% had responded to their most recent chemotherapy regimen. This difference might partly explain the different efficacy of gefitinib and erlotinib in ISEL and BR.21 studies. Thus, in many countries and regions, erlotinib has been approved as standard treatment for advanced NSCLC in second- or third-line settings. Although gefitinib was removed from the US market, it was approved in most Asian countries for advanced NSCLC.

EGFR TKIs combined with chemotherapy for advanced NSCLC in first-line setting

Erlotinib improves the cytotoxic effects of chemotherapy in preclinical models [Higgins *et al*. 2004]. So, it was proposed that combination of erlotinib and chemotherapy could further improve outcome of chemotherapy in patients with advanced NSCLC. Erlotinib in combination with chemotherapy as the first-line treatment of advanced NSCLC has been evaluated in two large multicenter, randomized, placebo-controlled clinical

Table 2. Erlotinib or gefitinib combined with chemotherapy as first-line therapy for patients with non-small cell lung cancer.

Trial	Study phase	Treatment	Number of patients	ORR (%)	PFS (months)	OS (months)
TRIBUTE [Herbst *et al*. 2005]	Phase III	Carbo/Pac+erlotinib 150 mg Carbo/Pac+placebo	526 533	21.5 19.3 $p = 0.36$	5.1 4.9 $p = 0.36$	10.6 10.5 $p = 0.95$
TALENT [Gatzemerier *et al*. 2007]	Phase III	Cis/Gem+erlotinib 150 mg Cis/Gem+placebo	579 580	31.5 29.9 p = NS	5.5 5.7 $p = 0.74$	9.9 10.2 $p = 0.49$
INTACT-1 [Giaccone *et al*. 2004]	Phase III	Cis/Gem+gefitinib 250 mg Cis/Gem+gefitinib 500 mg Cis/Gem+placebo	365 365 363	51.2 50.3 47.2 p = NS	5.8 5.5 6.0 $p = 0.76$	9.9 9.9 10.9 $p = 0.46$
INTACT-2 [Herbst *et al*. 2004]	Phase III	Carbo/Pac+gefitinib 250 mg Carbo/Pac+gefitinib 500 mg Carbo/Pac+placebo	345 347 345	30.4 30.0 28.7 p = NS	5.3 4.6 5.0 $p = 0.06$	9.8 8.7 9.9 $p = 0.64$

ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival; Cis, cisplatin; Carbo, carboplatin; Gem, gemcitabine; Pac, paclitaxel.

trials (Table 2). Two platinum-based doublets (carboplatin plus paclitaxel or cisplatin plus gemcitabine) were tested in combination with erlotinib in the Tarceva® Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) and Tarceva® Lung Cancer Investigation (TALENT) trials, respectively. In the TRIBUTE trial [Herbst *et al*. 2005], 1059 patients were randomized to receive either erlotinib or placebo combined with up to six cycles of carboplatin and paclitaxel, followed by maintenance erlotinib. The results revealed that addition of erlotinib into doublet chemotherapy did not improve efficacy. The median survival was 10.6 months in the erlotinib arm *versus* 10.5 months in the placebo arm (HR 0.995, 95% CI 0.86–1.16, $p = 0.95$). Time to progression (TTP) was 5.1 months for erlotinib and 4.9 months in the placebo arm ($p = 0.36$). Subset analyses failed to demonstrate any significant improvement in OS by sex, race, histology, or EGFR expression. Also, in the TALENT trial (phase III study of erlotinib combined with cisplatin and gemcitabine in advanced NSCLC) there was no statistically significant difference in any outcome, with a median survival time of 301 days *versus* 309 days. Therefore, there was no clinical benefit in either trial. There was also no clinical benefit when gefitinib was combined with chemotherapy in either of the following two similar trials: Iressa® NSCLC Trial Assessing Combination Therapy (INTACT)-1 (cisplatin plus gemcitabine) and INTACT-2 (carboplatin plus paclitaxel).

Two hypotheses have been proposed as most likely explanations of these negative results, as follows: (1) a negative interaction occurs between EGFR TKIs and cytotoxic agents when they are given concurrently [Gandara and Gumerlock, 2005]; (2) there was no patient selection for these trials. With regard to the first hypothesis, initial evidence has shown that EGFR TKIs can cause cell cycle arrest and accumulation of G1 tumor cells. This could interfere with cell-cycle-specific (S and G2/M phase) cytotoxicity of cytotoxic agents. Recent work also suggested that NSCLC patients with the EGFR mutation obtained better clinical outcome when treated with EGFR TKIs than those without the mutation. Thus, in these trials, lack of patient selection based on biomarkers may also contribute to negative results. These two hypotheses need to be further validated in clinical trials.

In conclusion, all of the first-line trials (Table 2) demonstrated that concurrent combination of EGFR TKIs and chemotherapy is not recommended as first-line treatment for advanced NSCLC.

Sequential use of chemotherapy and EGFR TKIs has been tested as alternative method to combine chemotherapy with EGFR-TKIs in the first-line setting. FAST-ACT (First-line Asian Sequential Tarceva And Chemotherapy Trial) was a phase II study to test the sequential use of erlotinib [Mok *et al*. 2009b]. In this trial, 154 unresected patients were randomized to receive either erlotinib 150 mg daily or placebo on days 15–28 in a 4-week treatment cycle with gemcitabine/platinum (GC) combination on days 1 and 8. The primary

endpoint was nonprogression rate (NPR) at 8 weeks. There was no significant difference in NPR in either of the two treatment arms (80.3% for the GC–erlotinib group, 76.9% for the GC–placebo group); however, PFS was significantly longer in the GC–erlotinib group than in the GC–placebo group (GC–erlotinib 29.4 weeks *versus* GC–placebo 23.4 weeks, adjusted HR 0.47, $p = 0.0002$). This encouraging result prompted the initiation of a large randomized phase III clinical trial of sequential use of erlotinib: FAST-ACT II. This trial is still ongoing.

Compared with FAST-ACT, the result of a trial from Hirsch and colleagues was discouraging [Hirsch *et al.* 2011]. A total of 143 patients were randomly assigned to either erlotinib 150 mg daily orally until disease progression (PD) or to chemotherapy with paclitaxel 200 mg/m^2 intravenously (IV) and carboplatin dosed by creatinine clearance (area under the curve [AUC] 6) IV on day 1 intercalated with erlotinib 150 mg orally on days 2–15 every 3 weeks for four cycles followed by erlotinib 150 mg orally until PD occurred (CT + erlotinib). The 6-month PFS rates (primary endpoint) were 26% and 31% for the two arms (CT + erlotinib and erlotinib alone, respectively). Both were less than the historical control of 45% ($p = 0.001$ and $p = 0.011$, respectively). Median PFS time were 4.57 and 2.69 months, respectively. Therefore, this trial does not support the sequential use of EGFR TKIs with chemotherapy. However, two issues have to be addressed when interpreting this result: (1) this trial selected patients on EGFR expression and/or gene copy number. Currently, EGFR mutation has been proved as the most reliable predictor for EGFR TKI treatment; (2) this is a phase II trial with small sample size. Considering the result of FAST-ACT, more clinical trials are warranted to test the sequential use of EGFR TKIs with chemotherapy.

Erlotinib or gefitinib as first-line treatment for unselected chemonaïve advanced NSCLC in phase II trials

Several phase II clinical trials have investigated the efficacy of TKIs as front-line therapy because of their encouraging results in second- and third-line treatment in patients with advanced NSCLC (Table 3).

Giaccone and colleagues reported a phase II trial in which single-agent erlotinib was administered as frontline therapy [Giaccone *et al.* 2006]. In this trial, 53 chemonaïve patients with advanced NSCLC were enrolled. The response rate was 22.7%, median TTP was 84 days and median OS was 391 days. Erlotinib was well tolerated and its main AEs were mild-to-moderate skin rash and diarrhea. Tissue samples were available in 29 patients for EGFR analysis and seven patients harbored positive EGFR mutation. Among them, four responded to erlotinib and one obtained long-lasting stable disease.

Lee and colleagues reported the efficacy of erlotinib as first-line therapy in Asian patients: in this trial, 24 patients who were not eligible for chemotherapy were enrolled [Lee *et al.* 2009]. The overall response rate was 21%. Median PFS and survival time were 1.5 and 3.2 months, respectively. The most common toxicities were skin rash (38%) and pruritus (38%). Severe or grade 3 toxicity included mucositis recorded in two patients and elevated enzyme in two patients. No grade 4 toxicity was observed. All responders were nonsmokers and had adenocarcinoma. EGFR mutation status analysis demonstrated that partial response was observed in two out of three patients (67%) with EGFR-activating mutation, but one in nine (11.1%) having wildtype EGFR.

A Japanese phase II study [Niho *et al.* 2006] and a clinical trial that was performed in Taiwan [Yang *et al.* 2008] also demonstrated that in unselected NSCLC, erlotinib or gefitinib seemed not be an appropriate treatment as first-line monotherapy (Table 3).

While these phase II trials did not obtain promising results when erlotinib or gefitinib were administered as first-line monotherapy for unselected advanced NSCLC patients, they did suggest that EGFR-mutant lung cancers are a distinct class of NSCLCs and this subgroup achieved better clinical outcomes when TKIs were taken as first-line therapy.

In addition, some trials have evaluated EGFR TKIs in unselected chemonaïve patients with poor performance. A phase II study (S0341) evaluated the efficacy and tolerability of single-agent erlotinib in unselected chemonaïve patients with advanced NSCLC and a performance status (PS) of 2 [Hesketh *et al.* 2008]. There were 81 patients enrolled in the study and the observed response rate was only 8%. PFS and median survival time were 2.1 months (95% CI 1.5–3.1) and 5 months (95% CI 3.6–7.2), respectively. With an overall disease control rate of 42% and median survival of 5 months, results are comparable to those

Table 3. Epidermal growth factor receptor tyrosine kinase inhibitors as first-line treatment for patients with advanced non-small cell lung cancer.

Study	Study phase	Treatment	Number of patients	ORR (%)	Median PFS/TTP	Median OS
Giaccone *et al.* [2006]	Phase II	Erlotinib	53	22.7	84 days	391 days
Lee *et al.* [2011]	Phase II	Erlotinib	24 (ineligible for chemotherapy)	21	1.5 months	3.2 months
Niho *et al.* [2006]	Phase II	Gefitinib	40	30	NA	13.9 months
Yang *et al.* [2008]	Phase II	Gefitinib	106	50.9	5.5 months	22.4 months

PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; OS, overall survival.

achieved with chemotherapy in this population. Another phase II trial has compared gefitinib to best supportive care (BSC) in patients with poor performance (2–3) unfit for chemotherapy [Goss *et al.* 2009]. The response of gefitinib in this unselected population was only 6%. No improvement of PFS or OS was observed. Thus, there is no evidence to support the use of EGFR TKIs as first-line treatment for unselected patients with poor performance.

The INVITE trial (gefitinib *versus* vinorelbine in chemotherapy-naïve elderly patients with advanced non-small cell lung cancer) has compared gefitinib with vinorelbine in unselected patients over 70 years old [Crino *et al.* 2008]. No significant differences in response rate, PFS, or OS were observed between treatments, although gefitinib was better tolerated. Thus, in this elderly unselected population, no evidence was found to support first-line treatment of EGFR-TKIs.

Erlotinib or gefitinib *versus* chemotherapy in EGFR-mutant patients as first-line therapy

The IPASS study

The IPASS study (Iressa Pan-Asia study) was a multicenter, phase III, randomized study to compare gefitinib and carboplatin plus paclitaxel as first-line treatment in clinically selected patients in east Asia [Mok *et al.* 2009a]. There were 683 patients who provided tumor samples and EGFR mutation data for 437 patients could be evaluated (Table 4). Of the 437 evaluated samples, 261 (59.7%) were harboring the EGFR mutation. In this EGFR mutation subgroup, response rate was 71.2% for gefitinib *versus* 47.3% for carboplatin plus paclitaxel ($p < 0.001$). In the EGFR-mutation group, median PFS was 9.5 months for gefitinib and 6.3 months for carboplatin plus paclitaxel (HR 0.48, 95% CI 0.36–0.64, $p < 0.001$). Median OS was not significantly different according to EGFR mutation status (21.6 months for gefitinib and 21.9 months for chemotherapy). Gefitinib as compared with carboplatin plus paclitaxel was associated with a lower rate of grade 3 or 4 AEs. The most common toxicity associated with gefitinib was rash or acne (66.2% of patients) and diarrhea (46.6%). Gefitinib compared with chemotherapy also improved quality of life assessed by the FACT-L (Functional Assessment of Cancer Therapy–Lung) questionnaire and by scores on the TOI (Trial Outcome Index). The IPASS study highlights that EGFR-mutant lung cancer is a distinct subgroup and that TKI therapy for this group is feasible and effective.

Subsequent studies

Following IPASS, several trials were conducted to compare TKI therapy with chemotherapy for EGFR mutant patients (Table 4).

The First-Signal study was a clinical trial performed in South Korea, which had a similar design to IPASS, and the results were also similar. This trial suggested that IPASS was reproducible and the EGFR mutation was the most reliable predictor to EGFR TKIs treatment.

Two trials compared first-line gefitinib *versus* chemotherapy for exclusive EGFR mutant lung cancers. The NEJ002 study [Maemondo *et al.* 2010] comprised 230 EGFR-mutant patients who were randomly assigned to receive gefitinib or carboplatin plus paclitaxel. The primary endpoint was PFS; secondary endpoints included OS, response rate, and toxic effects. In the planned interim analysis of data for the first 200 patients, the gefitinib group had a significantly longer median PFS (10.8 months, *versus* 5.4 months in the chemotherapy group; HR 0.30, 95% CI 0.22–0.41, $p < 0.001$), as well as a higher response rate (73.7% *versus* 30.7%,

Table 4. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors *versus* chemotherapy as first-line treatment for EGFR mutant patients.

Study	Study phase	Population	Treatment (number of patients)	ORR (%)	Median PFS/TTP (months)	Median OS (months)
IPASS [Mok *et al*. 2009a]	Phase III	EGFR mutation+	Gefitinib (132) Carbo+Pac (129)	71.2 47.3 $p < 0.001$	9.5 6.3 $p < 0.001$	21.6 21.9 $p = 1.00$
First-Signal [Lee *et al*. 2009]	Phase III	EGFR mutation+	Gefitinib Gem+Cis	84.6 37.5 $p = 0.002$	8.4 6.7 $p = 0.084$	30.6 26.5 $p = 0.648$
NEJSG002 [Maemondo *et al*. 2010]	Phase III	EGFR mutation +	Gefitinib (115) Carbo+Pac (115)	73.7 30.7 $p < 0.001$	10.8 5.4 $p < 0.001$	30.5 23.6 $p = 0.31$
WJTOG3405 [Mitsudomi *et al*. 2010]	Phase III	EGFR mutation +	Gefitinib (88) Cis+Doc (89)	62.1 32.2 $p < 0.0001$	9.2 6.3 $p < 0.0001$	30.9 NA $p = 0.211$
OPTIMAL [Zhou *et al*. 2011]	Phase III	EGFR mutation +	Erlotinib (82) Carbo+Gem (72)	83 36 $p < 0.0001$	13.1 4.6 $p < 0.0001$	NA NA $p =$ NS
EURTAC [Rosell *et al*. 2011]	Phase III	EGFR mutation +	Erlotinib Carbo/Cis+Doc/Gem	58 15 $p < 0.0001$	9.7 5.2 $p < 0.0001$	22.9 18.8 $p = 0.41$

PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; OS, overall survival; Cis, cisplatin; carbo, carboplatin; Pac, paclitaxel; Doc, docetaxel; Gem, gemcitabine.

$p < 0.001$). There was no significant difference in median OS, which was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group ($p = 0.31$). The most common AEs in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia, anemia and appetite loss were more common. One patient receiving gefitinib died from interstitial lung disease.

The WJTOG3405 trial [Mitsudomi *et al*. 2010] was similar in design to NEJ002, although the first-line chemotherapy was different (cisplatin plus docetaxel). The result was similar to NEJ002. In EGFR-mutant lung cancer patients, the objective response rate was 62.1% (36 of 58 patients) in the gefitinib group and 32.2% in the cisplatin plus docetaxel group ($p < 0.0001$). Median PFS was also longer in the gefitinib group compared with chemotherapy group (9.2 months *versus* 6.3 months, $p < 0.0001$).

OPTIMAL was a randomized phase III trial conducted in China, comparing erlotinib (150 mg/day, $n = 82$) to gemcitabine (1000 mg/m^2, D1,8, every 3 weeks) plus carboplatin (AUC = 5, $n = 72$) in advanced NSCLC patients with positive EGFR mutation. Its results were first presented at the European Society of Medical Oncology conference in 2010 [Zhou *et al*. 2011]. The primary endpoint was PFS, and secondary endpoints included OS, quality of life, and response rate. Erlotinib was significantly superior to chemotherapy in terms of PFS with median PFS of 13.1 months *versus* 4.6 months (HR 0.16, 95% CI 0.10–0.26, $p < 0.0001$). Response rate more than doubled in the erlotinib arm (83% *versus* 36%). Erlotinib proved to be better tolerated than chemotherapy. The subgroup analysis showed that almost all subgroups (gender, histology, smoking status) obtained better clinical benefit from erlotinib than from chemotherapy.

Erlotinib *versus* chemotherapy (cisplatin or carboplatin plus gemcitabine or docetaxel) in the first-line setting for EGFR-mutant patients was compared in the EURTAC trial [Rosell *et al*. 2011]. The planned interim analysis, presented at the American Society of Clinical Oncology (ASCO) conference in 2011, showed that when compared with platinum-based chemotherapy, erlotinib significantly extended PFS in the EGFR-mutant patients (9.7 *versus* 5.2 months). Response rate was also higher in the erlotinib group (58% *versus* 15% of chemotherapy group). There was also a better safety profile consistent with previous erlotinib studies.

Based on results from OPTIMAL and EURTAC studies there are now steps being taken for health authorities to extend the indication for erlotinib to include first-line treatment for patients with advanced NSCLC whose tumors harbor EGFR-activating mutations. The authors believe erlotinib should be used as first-line treatment of advanced NSCLC in patients with positive EGFR mutation. It is important to test EGFR genotyping in advanced NSCLC patients and it should become our daily practice.

It is also important to note that all of the large phase III trials mentioned above did not achieve OS benefit; however, given the poor prognosis of NSCLC with median survival less than 1 year, a valid surrogate endpoint such as PFS would be unaffected by the use of second-line therapy and can be assessed much sooner, leading to decreased cost and more timely approval of new treatments. Moreover, the PFS difference is substantial among groups; thus, facilitating interpretation of results into clinical practice.

Erlotinib or gefitinib as maintenance treatment after chemotherapy

Although second-line treatment for advanced NSCLC has been established, nearly 50% of patients will not be able to receive second-line therapy, mainly because of the rapid worsening of their clinical condition [Hensing *et al*. 2005]. One of the strategies that has been extensively studied to improve clinical outcome is maintenance therapy, which was defined as 'any treatment that is given to keep cancer from progressing after it has been successfully controlled by the appropriate first-line therapy' [Gridelli *et al*. 2009]. Unlike second-line therapy, which is applied when a tumor progresses, maintenance therapy is usually used when the tumor has been successfully controlled, whether it is stable disease, complete response, or partial response.

The Sequential Tarceva in Unresectable NSCLC (SATURN) trial investigated maintenance erlotinib compared with placebo in patients who did not experience PD after four cycles of platinum-based doublet chemotherapy. The primary endpoints were PFS in the intent-to-treat patient population and in those with EGFR-protein expression by immunohistochemistry. A total of 1949 patients were screened and given platinum-based chemotherapy and 889 (45%) patients who did not experience PD and who met the eligibility criteria were randomized to erlotinib (n = 438) or placebo (n = 451) arms. Patients in the erlotinib arm experienced significantly longer PFS and OS (Table 5). The most common grade 3 toxicities observed in the erlotinib and placebo arms included skin rash (9% and 0%, respectively) and diarrhea (2% and 0%, respectively). The majority of the patients in both arms of the study received poststudy therapy (71% *versus* 72%), including EGFR TKIs, taxanes, antimetabolites, antineoplastic agents, and platinum agents. Subgroup analysis showed that almost all subgroups of different clinical features obtained clinical benefit from erlotinib maintenance. While PFS was prolonged by erlotinib maintenance regardless of the response to prior chemotherapy, a significant OS benefit was only observed in patients with stable disease after first-line chemotherapy. A possible explanation is that patients with stable disease after first-line chemotherapy are more likely to have tumors that are resistant to cytotoxic agents, and therefore they may benefit from agents with different mechanisms of action such as the EGRF inhibitor erlotinib [Coudert *et al*. 2011].

The ATLAS study had a similar design to the SATURN trial. However, the initial four cycles of chemotherapy were combined with bevacizumab. Therefore, bevacizumab was given to both the erlotinib maintenance arm and the control arm [Miller *et al*. 2009]. Similar to the result of SATURN, the PFS was significantly improved by erlotinib plus bevacizumab maintenance therapy (4.8 *versus* 3.7 months).

At the 2011 ASCO conference, a Chinese oncologist reported another important clinical trial of gefitinib as maintenance therapy [Zhang *et al*. 2011]. The study included 296 patients with advanced NSCLC who were randomized to either gefitinib (n = 148) or placebo (n = 148) after completing four cycles of first-line platinum-based doublet chemotherapy without progression/unacceptable toxicity. Median duration of follow up was 16.8 months. Demography was balanced between treatments; overall, 54.1% of patients were never smokers, 70.6% had adenocarcinoma, and 40.9% were female. For gefitinib *versus* placebo group, ORR was 23.6% *versus* 0.7% (odds ratio = 54.1, 95% CI 7.17–408, p = 0.0001), and median PFS was 4.8 *versus* 2.6 months (HR 0.42, 95% CI 0.32–0.54, p < 0.0001). There was no significant difference for OS (18.7 *versus* 16.9 months; HR 0.84, 95% CI

Table 5. Erlotinib or gefitinib as maintenance therapy.

Study	Study phase	First-line therapy	Maintenance	Median PFS/TTP	Median OS
SATURN [Cappuzzo *et al.* 2010]	Phase III	Platinum-based doublets	Erlotinib Placebo	12.3 weeks 11.1 weeks $p < 0.0001$	12.0 months 11.0 months $p = 0.0088$
ATLAS [Miller *et al.* 2009; Kabbinavar *et al.* 2010]	Phase III	Platinum-based chemo+Bev	Bev+erlotinib Bev+placebo	4.8 months 3.7 months $p = 0.006$	15.9 months 13.9 months $p = 0.2686$
INFORM [Zhang *et al.* 2011]	Phase III	Platinum-based doublets	Gefitinib Placebo	4.8 months 2.6 months $p < 0.0001$	18.7 months 16.9 months $p = 0.2608$

PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; OS, overall survival; Bev, bevacizumab.

0.62–1.14, $p = 0.2608$). Consistent with other trials, patients with EGFR mutation benefited the most from gefitinib maintenance therapy (PFS 16.6 *versus* 2.8 months; HR 0.17, 95% CI 0.07–0.42, $p < 0.0001$). The most common AEs (any grade) with gefitinib were rash (49.7%), diarrhea (25.2%), and alanine transaminase increase (21.1%) which were generally mild/moderate. This trial suggests that gefitinib was well tolerated as maintenance treatment after first-line chemotherapy.

Conclusion

Randomized studies have confirmed the role of first-line erlotinib in patients with advanced NSCLC. The implication of these results in clinical practice might represent a new treatment paradigm by replacing standard chemotherapy in the first-line setting, which has played an unopposed leading-actor role in the last few decades. There is no doubt that NSCLC patients harboring positive EGFR mutations have a biologically different entity that requires personalized treatment strategies, including the use of EGFR TKIs. However, evidence shows that concurrent combination of chemotherapy and EGFR TKIs is not recommended.

The approach to maintenance therapy has been extensively studied in patients with advanced NSCLC. Study results show that erlotinib maintenance therapy may be used in those without PD after four to six cycles of first-line chemotherapy. Based on the results of the pivotal SATURN trial, erlotinib as monotherapy has recently been approved for patients with advanced NSCLC with nonprogressive (US Federal Drug Administration) or stable disease (European Medicines Agency) after first-line platinum-based initial chemotherapy. Although it is not clear if all patients should receive maintenance therapy, those with a heavy residual disease burden and symptomatic disease may well benefit from the use of maintenance therapy. Gefitinib has been tested in maintenance setting and the results are promising; however, it is not yet approved for maintenance therapy.

Although both erlotinib and gefitinib are reversible EGFR TKIs and target the same kinase domain of EGFR, it remains to be explored whether or not they provide the same clinical benefit in treating advanced NSCLC. For example, erlotinib was dosed at its maximum-tolerated dose (MTD) [Shepherd *et al.* 2004], while gefitinib was dosed at about one third of its MTD in clinical practice. Second, results showed that erlotinib (the BR.21 study) prolonged OS but gefitinib (the ISEL study) did not. Furthermore, case studies showed that that an objective response or stable disease can be observed in a few patients who took erlotinib after treatment failure with gefitinib for advanced NSCLC [Yamamoto *et al.* 2010]. However, adequately powered, direct comparisons of gefitinib against erlotinib under the same clinical scenarios are lacking. There are no data at present to suggest that the efficacy of these two agents in advanced NSCLC is different.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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