U.S. Food and Drug Administration Approval Summary: Erlotinib for the First-Line Treatment of Metastatic Non-Small Cell Lung Cancer With Epidermal Growth Factor Receptor Exon 19 Deletions or Exon 21 (L858R) Substitution Mutations

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Erlotinib • EGFR mutations • Lung cancer • FDA

ABSTRACT

On May 14, 2013, the U.S. Food and Drug Administration approved erlotinib (Tarceva, Astellas Pharma Inc., Northbrook, IL, <http://www.us.astellas.com/>) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. This indication for erlotinib was approved concurrently with the cobas EGFR Mutation Test (Roche Molecular Systems, Inc., Basel, Switzerland, <http://www.molecular.roche.com>), a companion diagnostic test for patient selection. The approval was based on clinically important improvements in progression-free survival (PFS) and objective response rate (ORR) and an acceptable toxicity profile demonstrated in a multicenter, open label trial enrolling 174 patients with metastatic NSCLC whose tumors had EGFR mutations as determined by a laboratory-

developed test. Patients were randomized (1:1) to receive erlotinib (150 mg/day) or platinum-based doublet chemotherapy. The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival (OS) and ORR. Superior PFS (hazard ratio [HR] 0.34; 95% confidence interval [CI]: 0.23, 0.49; $p < .001$) and ORR (65% vs. 16%) were observed in the erlotinib arm. Median PFS was 10.4 months and 5.2 months in the erlotinib and chemotherapy arms, respectively. There was no difference in OS (HR 0.93; 95% CI: 0.64, 1.35) with median OS of 22.9 months and 19.5 months in the erlotinib and chemotherapy arms, respectively. The most frequent ($\geq 30\%$) adverse reactions in the erlotinib-treated patients were rash, diarrhea, asthenia, cough, dyspnea, and decreased appetite. The most frequent ($\geq 5\%$) grade 3 and 4 adverse reactions were rash and diarrhea. *The Oncologist* 2014;19:774–779

Implications for Practice: In this report, we present key information on the U.S. Food and Drug Administration approval of erlotinib for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. We discuss the data supporting the approval decision, highlighting the importance of molecular enrichment in establishing the effectiveness of erlotinib as first-line therapy in metastatic non-small cell lung cancer.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the U.S., with an estimated number of new cases of over 220,000 and approximately 160,000 deaths in 2012 [1]. Approximately 85% of cases are non-small cell lung cancer (NSCLC), the majority of which present as advanced disease (stage IIIB or IV) at the time of diagnosis [1]. The median survival of patients with advanced NSCLC with supportive care is approximately 3–6 months [2]. Standard systemic treatment for patients with advanced

NSCLC in an unselected population consists of platinum-based doublet chemotherapy, with response rates of approximately 30% and a median survival of approximately 10 months [3–5].

Epidermal growth factor receptor (EGFR), also known as HER1, belongs to the ErbB or human epidermal receptor family of tyrosine kinase growth factor receptors; EGFR signaling mediates tumor proliferation, invasion, metastasis, resistance to apoptosis, and angiogenesis [6]. EGFR mutations are

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present in approximately 10% of NSCLC patients in the U.S. [7]. Preclinical studies have shown that certain EGFR mutations are oncogenic and can transform both fibroblasts and lung epithelial cells in the absence of exogenous epidermal growth factor, promoting tumor formation in immunocompromised mice [8]. The most common EGFR-activating mutations are deletions in exon 19 (45%) and a point mutation (L858R) in exon 21 (40%–45%) [9]. Patients with EGFR-activating mutations are more likely to have distinct clinicopathologic features such as female sex, never or light smokers, Asian origin, and adenocarcinoma histology [10].

Erlotinib (Tarceva) is an EGFR tyrosine kinase inhibitor (TKI), approved in the U.S. for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (2004), for maintenance in patients with locally advanced or metastatic NSCLC whose disease had not progressed after four cycles of platinum-based first-line chemotherapy (2010), and in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer (2005).

Early evidence of the activity of EGFR TKI therapy in first-line treatment of patients with NSCLC came from the Iressa Pan-Asia Study (IPASS), in which 1,217 patients in East Asia (never smokers and light ex-smokers) were randomly assigned (1:1) to receive gefitinib or carboplatin plus paclitaxel [11]. Gefitinib was associated with prolongation of investigator-assessed progression-free survival (PFS) in this clinically enriched patient population. In an exploratory post hoc biomarker analysis of IPASS, PFS appeared longer for gefitinib in the subgroup of patients with EGFR exon 19 deletions and exon 21 (L858R) substitution mutations, suggesting that the presence of these mutations may be a predictor of response to gefitinib [12]. Subsequent trials with gefitinib in patients prospectively enriched for the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations showed a similar trend [13, 14]. The role of erlotinib in this setting was investigated in OPTIMAL, an open-label, multicenter, randomized (1:1) trial conducted in China comparing the efficacy of erlotinib to carboplatin plus gemcitabine in a molecularly enriched population of 165 patients receiving first-line treatment for NSCLC with either an exon 19 deletion or an exon 21 (L858R) substitution. The reported investigator-assessed PFS was longer for the erlotinib arm compared with the chemotherapy arm (hazard ratio [HR] 0.16; 95% confidence interval [CI]: 0.10, 0.26) with a median PFS of 13.1 months in the erlotinib arm and 4.6 months in the chemotherapy arm [15]. The trial discussed in this report supporting the FDA approval of erlotinib built on these experiences to test the hypothesis that the presence of EGFR exon 19 deletions and exon 21 (L858R) substitution mutations can predict a superior response, as compared with standard chemotherapy, in a primarily European population of patients with previously untreated metastatic NSCLC.

TRIAL DESIGN

The U.S. Food and Drug Administration (FDA) reviewed a single investigator-sponsored trial titled “European Tarceva versus Chemotherapy (EURTAC).” EURTAC was a randomized (1:1), open-label trial in patients with metastatic NSCLC whose tumors harbored EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as determined by a laboratory-

developed test (LDT). The test was performed on laser-capture microdissected tumor specimens at a central laboratory and was comprised of initial Sanger sequencing for determination of EGFR mutation status followed by confirmatory testing by length analysis of fluorescently labeled polymerase chain reaction (PCR; GeneScan) for exon 19 deletions and TaqMan-based PCR (Applied Biosystems, Foster City, CA, <http://www.appliedbiosystems.com>) for L858R mutations in exon 21. Other key eligibility requirements were the presence of measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and no prior systemic therapy for metastatic disease.

Patients were randomly allocated to receive erlotinib (150 mg once daily) or four cycles of a platinum-based doublet chemotherapy (cisplatin or carboplatin plus gemcitabine or docetaxel) until disease progression, unacceptable toxicity, or death. Randomization was stratified by ECOG performance status (0 vs. 1 vs. 2) and EGFR mutation type (exon 19 deletions vs. exon 21 L858R substitution).

The primary endpoint of the trial was investigator-assessed PFS defined as the time from randomization to the first occurrence of progressive disease or death from any cause. Key secondary efficacy endpoints were the investigator-assessed objective response rate (ORR) and overall survival (OS). The EURTAC trial was designed with 80% power to demonstrate a HR of 0.6 at a two-sided significance level of .05. The underlying assumptions were a median PFS of 10 months in the erlotinib arm compared with 6 months in the chemotherapy arm at the time of primary analysis with 135 PFS events. There was no prespecified plan for adjustment for analyses of secondary endpoints.

The trial was amended on June 26, 2009, to include a plan for an independent review committee (IRC) to assess PFS and ORR. Approximately 25% of the 174 patients in the intent-to-treat analysis did not have adequate scans available for IRC review. At the FDA’s request, the trial was further amended to include a plan for retrospective testing of available tumor samples using the cobas EGFR Mutation Test, and based on these data, a premarket application (PMA) was submitted to the Center for Devices and Radiologic Health to support approval of this test as a companion diagnostic test. The PMA contained comparative analyses of the analytic performance of the cobas EGFR Mutation Test to two reference sequencing methods and a bridging study assessing the concordance of the cobas EGFR Mutation Test to the LDT.

RESULTS

A total of 1,275 patients were screened at 45 centers in Spain, France, and Italy, and 1,044 patients had tumor specimens available for determination of mutation status and met other eligibility criteria. A total of 225 (22%) patients were identified as having tumor mutations with an exon 19 deletion or an exon 21 (L858R) substitution mutation. Between February 15, 2007, and January 3, 2011, 174 patients with one of these mutations were randomly allocated to chemotherapy ($n = 88$) or erlotinib ($n = 86$). Except for gender, baseline demographics and stratification factors were similar between the two treatment arms (Table 1). The most frequent chemotherapy combination was gemcitabine plus cisplatin (41%) followed by gemcitabine plus carboplatin (31%). The median duration of treatment was

Table 1. Patient demographics and baseline characteristics

Characteristic	Erlotinib (n = 86)	Chemotherapy (n = 88)
Gender, n (%)		
Male	28 (33)	20 (23)
Female	58 (67)	68 (77)
Median age (range, years)	65 (24–82)	65 (29–82)
Country, n (%)		
France	21 (24)	18 (20)
Italy	11 (13)	8 (9)
Spain	54 (63)	62 (70)
ECOG performance status, n (%)		
0	27 (31)	31 (35)
1	47 (55)	45 (51)
2	12 (14)	12 (14)
Smoking status, n (%)		
Current smoker	7 (8)	12 (14)
Never smoker	57 (66)	63 (72)
Past smoker	22 (26)	13 (15)
Type of EGFR mutation, n (%)		
Exon 19 deletions	57 (66)	58 (66)
Exon 21 (L858R) substitution	29 (34)	30 (34)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Figure 1. Kaplan-Meier curves of progression-free survival in the intent-to-treat population.

Abbreviation: Chemo, chemotherapy.

9.6 months (0.3–43.5 months) for erlotinib-treated patients and 2.8 months (0.7–5.1 months) for chemotherapy-treated patients. Following investigator-determined disease progression, the majority (82%) of patients randomized to the chemotherapy arm received an EGFR TKI, predominantly erlotinib.

Efficacy

EURTAC demonstrated superior PFS for patients assigned to erlotinib treatment (HR 0.34; 95% CI: 0.23, 0.49; $p < .001$) compared with platinum-doublet chemotherapy. As shown in the Kaplan-Meier curves (Fig. 1), the curves separated at approximately 6 months and remained separated throughout follow-up. The median PFS was 10.4 months in the erlotinib arm and 5.2 months in the chemotherapy arm. In sensitivity

Figure 2. Kaplan-Meier curves of overall survival in the intent-to-treat population.

Abbreviation: Chemo, chemotherapy.

analyses using the IRC-determined PFS, similar treatment effects were observed. The final analysis of OS, conducted at the time of the final analysis of PFS following 109 deaths, showed no difference between the two treatment arms with HR of 0.93 (95% CI: 0.64, 1.35). The median survival was 22.9 months in the erlotinib arm and 19.5 months in the chemotherapy arm (Fig. 2). Objective response rates were 65% and 16% in the erlotinib and chemotherapy arms, respectively.

The FDA performed exploratory analyses in two subgroups defined by the underlying EGFR mutation as determined by the LDT. In both analyses, PFS was significantly improved for patients randomized to erlotinib, with an HR of 0.27 (95% CI: 0.17, 0.43) for the subgroup with exon 19 deletions and an HR of 0.52 (95% CI: 0.29, 0.95) in the subgroup with exon 21 (L858R) substitution mutation. Subgroup analyses of OS based on EGFR mutation demonstrated a HR of 0.94 (95% CI: 0.57, 1.54) in the subgroup with exon 19 deletions and a HR of 0.99 (95% CI: 0.56, 1.76) for the subgroup with exon 21 (L858R) substitution mutation.

Bridging Studies With cobas EGFR Mutation Test

Sufficient tumor samples were available from 134 (77%) patients enrolled in the EURTAC trial (69 patients in the erlotinib arm and 65 patients in the chemotherapy arm) to conduct retrospective testing using the cobas EGFR Mutation Test. For 87% of these patients ($n = 117$), the presence of an EGFR mutation in tumor samples was confirmed. Efficacy analyses performed in the subgroup of patients with cobas EGFR Mutation Test-confirmed mutations, based on investigator and on IRC assessment, were comparable to the results observed in the overall population.

Toxicity

Of the 174 patients enrolled in the EURTAC trial, 167 (96.0%) received at least one dose of protocol-specified therapy and were included in the analysis of safety: 83 patients who received chemotherapy and 84 patients who received erlotinib. Seven patients (4.0%) were excluded for the following reasons: six patients did not receive treatment (five received chemotherapy, and one received erlotinib) and one patient had no follow-up data (erlotinib).

Table 2. Per-patient incidence of adverse reactions occurring at a rate of at least 10% in either arm

Body system/adverse event	Chemotherapy (n = 83)		Erlotinib (n = 84)	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Gastrointestinal disorders				
Diarrhea	21	1	62	5
Nausea	42	5	29	1
Vomiting	24	5	14	0
Constipation	21	0	11	0
General disorders and administration site conditions				
Asthenia	71	21	58	6
Chest pain	12	0	18	1
Pyrexia	17	0	13	0
Mucosal inflammation	6	0	18	1
Skin and subcutaneous tissue disorders				
Rash	2	0	56	10
Alopecia	18	2	14	0
Dry skin	2	0	21	1
Pruritus	1	0	16	0
Acne	0	0	13	0
Respiratory, thoracic, and mediastinal disorders				
Cough	35	0	48	1
Dyspnea	29	4	45	8
Blood and lymphatic system disorders				
Anemia	46	4	14	1
Neutropenia	37	22	0	0
Leukopenia	16	6	2	0
Thrombocytopenia	12	12	1	0
Metabolism and nutrition disorders				
Decreased appetite	34	2	36	0
Musculoskeletal and connective tissue disorders				
Back pain	5	0	19	2
Arthralgia	6	1	13	1
Musculoskeletal pain	1	0	11	1
Infections and infestations				
Paronychia	0	0	14	0
Folliculitis	0	0	11	2
Eye disorders				
Conjunctivitis	0	0	18	0
Ear and labyrinth disorders				
Tinnitus	11	0	1	0

The most common adverse events, occurring in at least 10% of the safety-evaluable population, are summarized in Table 2. Premature termination of planned treatment because of adverse events occurred in 20.5% of patients in the chemotherapy arm and 14.3% of patients in the erlotinib arm. More patients in the chemotherapy group (49.4%) had modifications of the planned treatment (reduced or delayed) for adverse events compared with 36.9% of the erlotinib group. The most frequently reported adverse events resulting in dose modification for erlotinib-treated patients were rash (13.0%), diarrhea (10.0%), and asthenia (3.6%).

Serious adverse events were reported in 36.9% and 31.3% of patients in the erlotinib and chemotherapy arms, respectively. The most frequently reported serious adverse events, occurring in at least 2% of erlotinib-treated patients were pulmonary embolism (3.6%), back pain (2.4%), cardiac tamponade (2.4%), diarrhea (2.4%), dyspnea (2.4%), femoral neck fracture (2.4%), pneumonia (2.4%), and pneumonitis (2.4%). There were two deaths possibly related to erlotinib. One patient died on study day 114 from hepatotoxicity, following hospitalization on study day 113 with jaundice and elevated liver enzymes. A second patient died on day 129 from

interstitial lung disease; this patient developed dyspnea on day 24 with permanent discontinuation of erlotinib on day 25 following radiographic evidence of pneumonitis. The applicant assessed this death as remotely related to treatment.

DISCUSSION

The presence of certain mutations in EGFR can predict the response to EGFR TKIs [16]. In published reports, response rates to EGFR TKIs are generally higher than platinum-based chemotherapy in patients with NSCLC whose tumors harbor EGFR-activating mutations [7, 17]. The EURTAC trial tested this hypothesis in patients whose NSCLC contained EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In EURTAC, the 5.2-month increase in median PFS for erlotinib compared with platinum-doublet chemotherapy was both clinically important and statistically robust. The treatment effect was further supported by the approximately fourfold increase in ORR for patients on the erlotinib arm compared with the standard platinum-based doublet chemotherapy arm. Although the EURTAC trial did not demonstrate a statistically significant improvement in OS in the erlotinib arm as compared with chemotherapy, this may have been confounded by postprogression treatment with an EGFR-directed TKI, which in all but two cases involved subsequent erlotinib. The analysis of adverse drug reactions in the EURTAC trial did not identify new, clinically significant safety signals, and in the context of the efficacy results, the benefits of erlotinib outweighed its risks.

The strategy of enrolling a molecularly enriched subgroup of patients, as used in the EURTAC trial, was critical to demonstrating the effectiveness of erlotinib as first-line therapy in NSCLC. In this enriched population, large treatment effects on PFS and ORR for erlotinib over chemotherapy were clearly demonstrated, confirming the value of EGFR exon 19 deletions and exon 21 (L858R) substitution mutations in predicting the response to erlotinib in patients with metastatic NSCLC. In contrast to the EURTAC trial, multiple clinical trials [18–20], with four to six times the enrollment in EURTAC, failed to demonstrate the efficacy of erlotinib, as a single agent or as add-on to standard chemotherapy, in unselected populations of patients receiving first-line treatment for NSCLC. In the TRIBUTE trial [18], 1,059 patients receiving first-line treatment for advanced NSCLC were randomly allocated (1:1) to carboplatin-paclitaxel alone or in combination with erlotinib (150 mg daily). There was no evidence of improvement in OS (HR 0.99; 95% CI: 0.86, 1.16; $p = .95$), time to progression, or ORR between arms. In the TALENT trial [19], 1,137 patients with advanced chemotherapy-naïve NSCLC were randomly allocated (1:1) to receive six cycles of cisplatin-gemcitabine plus erlotinib at 150 mg daily or placebo. The trial demonstrated no improvement in OS, time to progression, or ORR with the addition of erlotinib to chemotherapy. The TORCH trial [20] was a randomized, open-label study in 760 patients with advanced NSCLC and was designed to show noninferiority in OS between the experimental arm of first-line erlotinib followed by cisplatin-gemcitabine at progression and the standard inverse sequence. The trial was terminated after the first planned interim analysis demonstrated inferiority of the experimental arm.

After a median follow-up of 24.3 months, OS was 11.6 months (95% CI: 10.2, 13.3) in the standard arm and 8.7 months (95% CI: 7.4, 10.5) in the experimental arm (adjusted HR = 1.24; 95% CI: 1.04, 1.47).

Two areas regarding optimal use of erlotinib require further study: whether efficacy varies by mutation subtype (exon 19 deletions or exon 21 substitution mutations) and whether erlotinib is also effective in the treatment of NSCLC containing other “sensitizing” mutations. Published reports suggest that the treatment effects of erlotinib or gefitinib on PFS and OS are greater in patients whose NSCLC contains EGFR exon 19 deletions compared with those containing exon 21 (L858R) substitution mutations [21]. The FDA conducted exploratory analyses in subgroups based on mutation subtype, a stratification variable at randomization, in the EURTAC trial. Although the point estimate of the treatment effect on PFS was greater in the 115 patients with EGFR exon 19 deletions (HR = 0.27; 95% CI: 0.17, 0.43) than in the 59 patients with exon 21 (L858R) substitution mutations (HR = 0.52; 95% CI: 0.29, 0.95), additional data will be needed to confirm this finding.

The EURTAC trial limited enrollment to patients whose tumors expressed EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, which together represent 85% of EGFR sensitizing mutations. Because patients with less common sensitizing EGFR mutations such as G719X (exon 18), VAIKEL insertion (exon 19), and L861X (exon 21) [22] were not enrolled, the safety and efficacy of erlotinib for the treatment of NSCLC with mutations other than EGFR exon 19 deletions and exon 21 (L858R) substitution mutations have not been established. Future trials exploring novel trial designs [23] should assess the safety and efficacy of erlotinib for uncommon EGFR mutations.

CONCLUSION

The approval of erlotinib for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions and exon 21 (L858R) substitution mutations marked the first approval of an EGFR inhibitor, and its associated companion diagnostic test, for this patient population. Progress in understanding the molecular drivers of NSCLC will likely lead to approval of more agents directed at specific mutations. Clinical trial designs for such agents should be based on the latest scientific evidence, focusing on appropriate patient populations and patient selection tools to ensure efficient use of resources and minimize discarding of effective anticancer therapies.

AUTHOR CONTRIBUTIONS

Conception/Design: Sean Khozin, Gideon M. Blumenthal

Provision of study material or patients: Sean Khozin

Collection and/or Assembly of data: Sean Khozin

Data analysis and interpretation: Sean Khozin, Gideon M. Blumenthal, Xiaoping Jiang, Kun He, Patricia Keegan

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DISCLOSURES

The authors indicated no financial relationships.

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For Further Reading:

Sarah B. Goldberg, Geoffrey R. Oxnard, Subba Digumarthy et al. Chemotherapy With Erlotinib or Chemotherapy Alone in Advanced Non-Small Cell Lung Cancer With Acquired Resistance to EGFR Tyrosine Kinase Inhibitors. *The Oncologist* 2013;18:1214–1220.

Implications for Practice:

Patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC) typically respond well to treatment with an EGFR tyrosine kinase inhibitor (TKI); however, acquired resistance eventually develops. It is unknown whether the continuation of the EGFR TKI along with initiation of chemotherapy results in improved patient outcomes compared to switching to chemotherapy alone. This article describes a retrospective study that compares these two practices, providing clinicians with information regarding the potential benefit to treating patients with chemotherapy plus erlotinib rather than chemotherapy alone after the development of TKI resistance. We found that continuing erlotinib with chemotherapy improves the response rate and is therefore a reasonable treatment option for patients with EGFR-mutant lung cancer acquired resistance to EGFR TKIs.