Clinical Cancer Research

FDA Approval of Gefitinib for the Treatment of Patients with Metastatic *EGFR* Mutation–Positive Non–Small Cell Lung Cancer

Dickran Kazandjian[1], Gideon M. Blumenthal[1], Weishi Yuan[2], Kun He[2], Patricia Keegan[1], and Richard Pazdur[1]

Abstract

On July 13, 2015, the FDA approved gefitinib (Iressa; AstraZeneca UK Limited) for the treatment of patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Concurrently, a labeling expansion of the *therascreen EGFR* RGQ PCR Kit (Qiagen) as a companion diagnostic test was approved. The approval was based on the results of a multicenter, single-arm, open-label clinical study of 106 treatment-naïve patients with metastatic *EGFR* mutation–positive NSCLC who received gefitinib, 250 mg daily, until disease progression or intolerable toxicity. The major efficacy outcome was RECIST v1.1 objective response rate (ORR). The blinded independent central review (BICR) ORR was 50% [95% confidence interval (CI), 41–59] with a median duration of response (DoR) of 6.0 months. Efficacy results were supported by a retrospective exploratory analysis of a subset of a randomized, multicenter, open-label trial on 1,217 patients with metastatic NSCLC. Of the patients randomized, 186 (15%) were retrospectively determined to be *EGFR* positive and evaluable for a BICR assessment. The HR for progression-free survival (PFS) was 0.54 (95% CI, 0.38–0.79), favoring gefitinib over platinum-doublet chemotherapy. The most common (≥20%) adverse reactions were skin reactions, increased aspartate and alanine aminotransferase, proteinuria, and diarrhea. Approximately 5% of patients discontinued treatment due to an adverse reaction. Given the safety profile and clinically meaningful ORR, DoR, and PFS, the benefit–risk analysis was deemed favorable for FDA approval. *Clin Cancer Res; 22(6); 1307–12. ©2016 AACR.*

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Editor's Disclosures

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CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the clinical trials and complex regulatory processes that led to the approval of gefitinib in July 2015, for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) that harbors specific types of epidermal growth factor receptor (*EGFR*) gene mutations. This approval highlights the importance of understanding the underlying biology of responders, which ultimately led to the resurrection of this drug in a molecularly enriched patient population.

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[1]Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA, Silver Spring, Maryland. [2]Office of Biostatistics, Center for Drug Evaluation and Research, FDA, Silver Spring, Maryland.

D. Kazandjian and G.M. Blumenthal contributed equally to this article.

Corresponding Author: Dickran Kazandjian, FDA, 10903 New Hampshire Avenue, WO22 2320, Silver Spring, MD 20993. Phone: 240-402-5272; Fax: 301-796-9849; E-mail: Dickran.kazandjian@fda.hhs.gov

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Introduction

Lung cancer is the second most common cancer and the leading cause of cancer-related death worldwide (1). Most cases of lung cancer are diagnosed at advanced stages, with stage IV associated with a 1% 5-year survival rate (1). In the past decade, molecular "driver" mutations have been identified, and small-molecule kinase inhibitors have been developed to target specific molecular aberrations (2–5).

Currently, FDA-approved targeted therapies in non–small cell lung cancer (NSCLC) exist for patients with *ALK* and *EGFR*

genomic alterations, and screening for the alterations is considered standard of care (6–14). One of the most studied "driver" pathways is the EGFR axis. *EGFR* kinase domain mutations are present in about 25% of NSCLC patients and are more common in females, never smokers patients of East Asian ancestry, and patients with adenocarcinoma histology. EGFR tyrosine kinase inhibitors (TKI), such as erlotinib (Tarceva; Astellas) and afatinib (Gilotrif; Boehringer Ingelheim), are FDA approved for the treatment of patients with metastatic NSCLC harboring *EGFR* exon 19 deletion or exon L858R substitution mutation.

EGFR is a receptor tyrosine kinase that, along with HER2, HER3, and HER4, belong to the ERBB family. Its natural ligands (EGF, TGFβ) bind and subsequently cause homo/heterodimerization and subsequent cascade activation involving the RAS, RAF, MEK, and MAPK pathways or the PI3K pathways, ultimately leading to cell proliferation, survival, invasion, and metastasis (15). Mutations in the tyrosine kinase region (ATP-binding pocket domain involving exons 18–21) lead to constitutive activation. Approximately 85% of all drug-sensitive mutations involve the L858R mutation or small internal deletions of exon 19. Exon 20 insertions are in general resistant to EGFR TKIs (16). L861Q and G719X mutations are less common and are thought to be intermediate in sensitivity to EGFR TKIs (17, 18). Drug-resistant mutations can be categorized as either primary or secondary (T790M in 60% of resistant cases; refs. 19, 20). Gefitinib is an orally active selective small-molecule inhibitor of the EGFR tyrosine kinase, which, upon binding (with 10 times higher affinity to sensitive mutations compared with wild type; ref. 21), is thought to interrupt mitogenic and survival signals responsible for oncogenesis (22).

Drug Development History

On July 13, 2015, the FDA approved gefitinib for the first-line treatment of patients with metastatic NSCLC whose tumors harbor *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. However, gefitinib's drug-development history began over a decade ago before advances in molecular biology led to the discovery of sensitizing mutations in the kinase domain of *EGFR*. Key events in the development and regulatory history of gefitinib are shown in Fig. 1. Based on preliminary results in objective response rate (ORR) of approximately 15% in a refractory unselected patient population, gefitinib initially received accelerated approval in 2003 under subpart H regulations as a monotherapy for the treatment of patients with advanced NSCLC after failure of both platinum-based and docetaxel therapies.

Following accelerated approval of gefitinib, the applicant (AstraZeneca) initiated three randomized studies to confirm clinical benefit. These studies were Iressa vs Best Supportive Care Randomized Evaluation of Effect on Symptom Endpoint (IBREESE), Iressa Survival Evaluation in Lung Cancer (ISEL; ref. 23), and Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST; ref. 24). The IBREESE was closed due to feasibility problems. The INTEREST trial was a noninferiority study of gefitinib compared with docetaxel in which superiority of gefitinib was not demonstrated. In ISEL, gefitinib failed to demonstrate a statistically significant improvement in overall survival versus placebo. As a result of ISEL, FDA approved updated labeling in June 2005 restricting use to patients, who in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. The FDA agreed to limit distribution under a risk management plan called the Iressa Access Program. Use was limited to patients who were currently or previously receiving and benefiting from gefitinib and previously enrolled patients or new patients in non–Investigational New Drug clinical trials approved by an Institutional Review Board prior to June 17, 2005. Subsequently, the applicant voluntarily withdrew the new drug application in April 2012.

Following the initial approval in 2003, knowledge of the underlying biology of *EGFR*-mutated NSCLC improved, leading to a better understanding of the patient population most likely to derive benefit from EGFR TKIs, and to new trials in molecularly or clinically enriched patient populations. A retrospective subgroup analysis of the IPASS trial suggested that the *EGFR* mutation status of a patient's tumor is predictive of gefitinib efficacy in Asian patients in the first-line setting (25). The approval of gefitinib in the European Union was based primarily on data from the IPASS study. Subsequently, the applicant conducted the Iressa Follow-Up Measure (IFUM) study to fulfill a commitment to the European Medicines Agency to address efficacy in non-Asian patients (26). The results of IFUM, supported by the retrospective subgroup analysis of *EGFR*-positive tumor samples in IPASS, were the basis of the current approval of gefitinib in patients with sensitizing *EGFR* mutations and are the focus of this approval summary.

Clinical Trial Design

The IFUM was a multicenter, single-arm, open-label clinical study of a total of 106 treatment-naïve patients with metastatic *EGFR* mutation–positive NSCLC who received gefitinib at a dose of 250 mg daily until disease progression or intolerable toxicity. The major efficacy outcome was ORR according to RECIST v1.1 as evaluated by both the blinded independent central review (BICR) and investigators, as well as duration of response (DoR). Eligible patients were required to have a deletion in *EGFR* exon 19 or L858R, L861Q, or G719X substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay, with 87 tumor specimens retrospectively tested using the *therascreen EGFR* RGQ PCR Kit.

The results were supported by a retrospective exploratory analysis of a subset of a randomized, multicenter, open-label trial (IPASS) conducted in patients with metastatic NSCLC with a histology of adenocarcinoma receiving first-line treatment. Patients were randomized (1:1) to receive gefitinib, 250 mg orally once daily, or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and ORR as assessed by the BICR. The subset population consisted of 186 of 1,217 (15%) patients determined to be *EGFR* positive by the *therascreen EGFR* RGQ PCR Kit who had radiographic scans available for a retrospective assessment by the BICR. In this subset, there were 88 gefitinib-treated patients and 98 carboplatin/paclitaxel-treated patients.

Efficacy

The baseline demographic and tumor characteristics of patients enrolled in the IFUM were as follows: median age of 65 years, white ethnicity (100%), female (71%), never smokers (64%), PS 0-1 (93%), adenocarcinoma histology (97%), *EGFR* exon 19 deletions (65%), L858R substitution (31%), L861Q

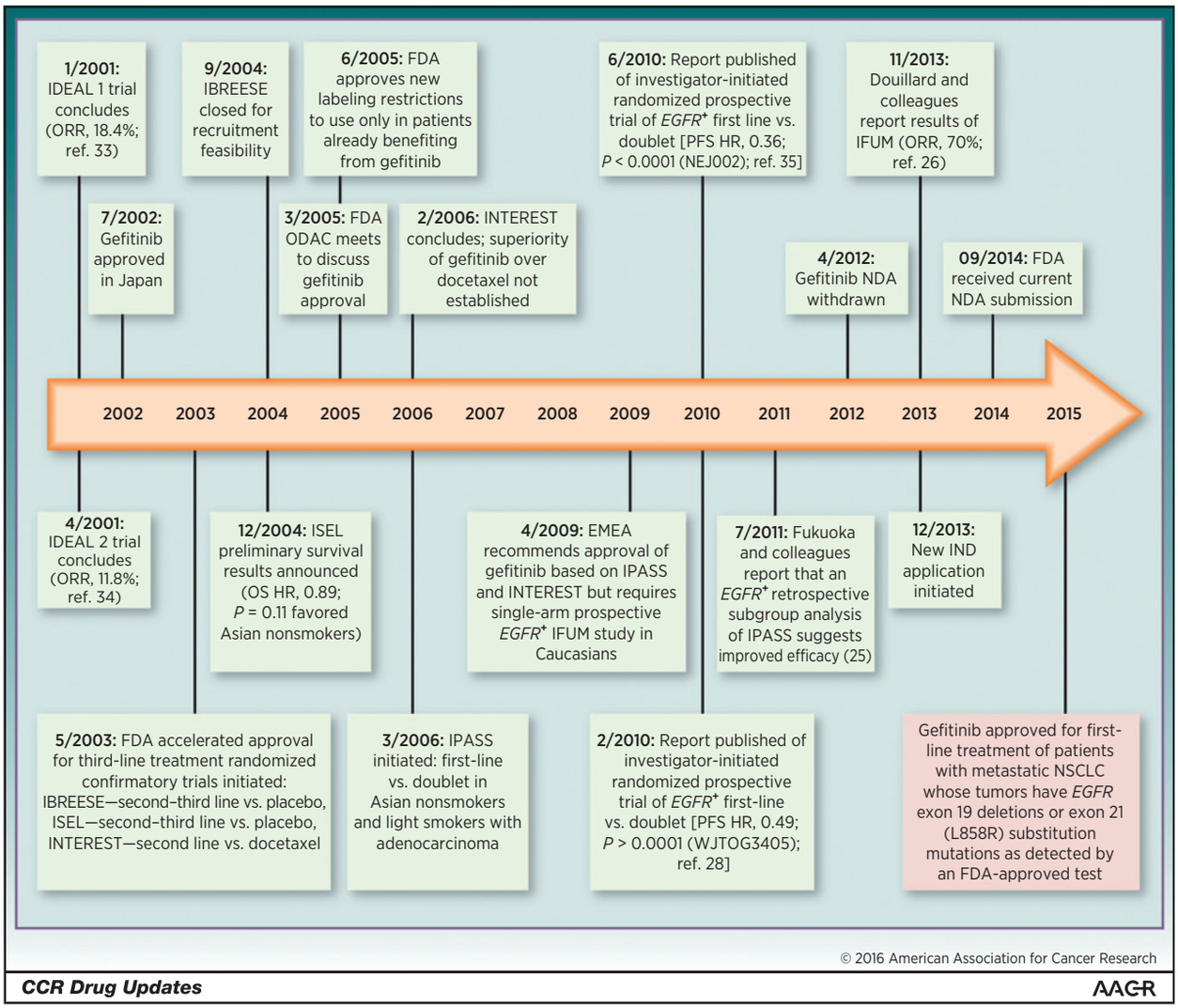

Figure 1.
Key events in gefitinib's development. EMEA, European Medicines Evaluation Agency; IND, investigational new drug; NDA, new drug application; ODAC, Oncology Drug Advisory Committee; OS, overall survival.

(2%; $n = 2$), and G719X (2%; $n = 2$) substitution mutations. The median duration of treatment (DoT) was 8 months. The ORR was 50% [95% confidence intervals (CI), 41%–59%] with a median DoR of 6.0 months (95% CI, 5.6–11.1) by BICR and ORR of 70% (95% CI, 61%–78%) with a median DoR of 8.3 months (95% CI, 7.6–11.3) by investigator assessment. The discrepancy between BICR and investigator was largely due to the fact that the BICR determined that 17 patients at baseline had none-valuable target lesions and were deemed nonresponders. Response rates were similar in *EGFR* exon 19 deletion and exon 21 L858R substitution mutation subsets. Both patients with tumors harboring G719X substitution mutations had partial responses, with DoR of at least 2.8 months and 5.6 months. Of the 2 patients with L861Q mutation, one had a partial response with a DoR of at least 2.8 months.

Baseline and tumor characteristics of the 186 patients included in the subset for the retrospective exploratory analysis from the IPASS were median age of 59 years, Asian ethnicity (100%), female (83%), never smokers (96%), adenocarcinoma histology (100%), and PS 0-1 (94%). The median DoT for gefitinib was 9.8 months. The PFS HR was 0.54 (95% CI, 0.38–0.79) with a median PFS of 10.9 months for the gefitinib-treated patients and 7.4 months for the carboplatin/paclitaxel-treated patients as assessed by BICR. In addition, the ORR for gefitinib-treated patients was 67% (95% CI, 56–77) versus 41% (95% CI, 31–51) for carboplatin/paclitaxel-treated patients based on BICR assessment. The median DoR was 9.6 months for gefitinib-treated patients versus 5.5 months for carboplatin/paclitaxel-treated patients.

Safety

Safety data were evaluated for common adverse reactions in the double-blind placebo- controlled trial of 1,692 patients (ISEL) who were randomized (2:1) to receive either gefitinib or placebo for the second- or third-line treatment of metastatic NSCLC. The ISEL was used as the basis for the safety evaluation because its

design with a placebo comparator made evaluation of adverse event incidence and attributability to gefitinib clearer. Of the 1,129 patients who received gefitinib, the most common (≥20%) adverse reactions were skin reactions (47%), aspartate aminotransferase (AST) increase (40%), alanine aminotransferase (ALT) increase (38%), proteinuria (35%), and diarrhea (29%). The most common (≥2%) grade 3 to 4 adverse reactions were proteinuria (4.7%), diarrhea (3.0%), ALT increase (2.4%), decreased appetite (2.3%), AST increase (2.0%), and skin reactions (2%). Approximately 5% of gefitinib-treated patients discontinued treatment due to an adverse reaction. The most frequent adverse reactions that led to discontinuation were nausea (0.5%), vomiting (0.5%), and diarrhea (0.4%).

Common along with serious and uncommon adverse drug reactions were evaluated in 2,462 patients with NSCLC who received gefitinib monotherapy in three randomized clinical studies (ISEL, INTEREST, and IPASS). Of the 2,462 patients who received gefitinib, the most common (≥20%) adverse reactions were diarrhea (35%), rash (34%), and decreased appetite (20%). The most common (≥2%) grade 3 to 4 adverse reactions were dyspnea (4%) and diarrhea (3%). Significantly serious adverse reactions from the pooled safety analysis included interstitial lung disease (1.3%), fatal hepatotoxicity (0.04%), and grade 3 ocular disorders (0.1% of patients).

Discussion

On July 13, 2015, gefitinib received FDA approval leading to the reintroduction of gefitinib to the U.S. market and providing patients with an additional option for first-line treatment of locally metastatic NSCLC whose tumors have *EGFR* exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

The efficacy of gefitinib in this patient population was demonstrated by an ORR of adequate magnitude and durability in a single-arm trial of patients prospectively determined to be *EGFR*-mutation positive, as well as a retrospective exploratory analysis based on the subgroup of the randomized trial (IPASS), which showed an adequate magnitude of ORR and PFS benefit and favorable benefit–risk profile over platinum-doublet therapy. The PFS results based on the subgroup from IPASS were supported by a literature review of two multicenter Japanese studies (NEJ002 and WJTOG3405; refs. 27, 28), in which gefitinib demonstrated improvement in ORR and PFS compared with platinum-doublet chemotherapy. A recent meta-analysis by the FDA showed that in advanced NSCLC, a drug with a large magnitude of effect on ORR may likely result in a large improvement in PFS (29).

Importantly, there was a 17% difference in ORR by the BICR when comparing IFUM with the IPASS retrospective analysis. The major reason for this was likely the previously mentioned discrepancy in IFUM between BICR- and investigator-assessed response rates, where 17 cases were unevaluable by BICR. If these 17 cases are removed from the denominator for the BICR ORR, the ORR becomes approximately 60% and closer to IPASS. Second, there are subtle differences in the two patient populations other than race and ethnicity. The IPASS consisted of 12% more females and 24% more never smokers, and the population had a 6-year younger median age.

Observed adverse events following administration of gefitinib appeared to be consistent with those observed with other approved EGFR TKIs. The recommended dose of 250 mg daily is below the maximum tolerated dose and thus led to few dose interruptions, modifications, or discontinuations. The FDA based the safety evaluation for common adverse events on the ISEL study because it was a randomized placebo-controlled trial leading to more accurate description of gefitinib's adverse reactions. The ISEL was a second/third-line study; however, when it was compared with the first-line studies, including IFUM and IPASS, no new safety signals were identified. For example, the most common adverse events (≥20%) in all trials, including the IFUM study,

Table 1. FDA benefit–risk analysis of gefitinib in the treatment of patients with metastatic *EGFR* mutation–positive NSCLC

Disease	**Patients with metastatic *EGFR*$^+$ NSCLC have a serious and life-threatening condition with historic median survival rates of 8 to 10 months with minimal available therapies.**
Unmet medical need	Patients with metastatic NSCLC whose tumors harbor *EGFR*-activating sensitizing mutations (typically exon 19 deletion and L858R substitution mutation) have few therapeutic options and are usually treated preferentially with EGFR tyrosine kinase inhibitors followed by standard cytotoxic chemotherapy. The currently available therapies include erlotinib and afatinib, which are associated with ORRs of 50% to 65%, median PFS of 6 to 9 months, and median overall survival of 2 to 3 years. However, more options for this patient population are needed given varying side effect profiles.
Clinical benefit	In a single-arm study conducted in patients with metastatic NSCLC who were prospectively selected based on *EGFR* status, an ORR of 70% and a median DoR of 8.3 months were observed. In a second randomized study, subgroup analysis of PFS based on *EGFR* status was associated with a 52% improvement in the risk of progression. Independent review committees in both studies confirmed the investigator-derived results. However, the benefit of gefitinib on rarer subtypes of *EGFR* mutations and alterations remains to be clarified. Patients with known insensitive mutations (T790M and exon 20 insertions) did not derive benefit with gefitinib treatment.
Risk	The most common adverse reactions and laboratory abnormalities in patients receiving gefitinib included skin reactions, ALT increases, diarrhea, decreased appetite, and emesis. Rare but clinically significant adverse reactions included hepatotoxicity, interstitial lung disease, diarrhea, and ocular disorders. These adverse reactions were managed with supportive measures and in a few cases were fatal. However, the incidence of fatal adverse reactions attributable to gefitinib was overall low (<1%). Gefitinib appears to have a better adverse reaction profile than conventional chemotherapy and a similar-to-better adverse reaction profile than other EGFR TKIs, likely because gefitinib is administered at the "optimal biologic dose" rather than at the MTD.
Uncertainties	The clinical benefit of gefitinib use in patients with rare *EGFR* mutation subsets is unknown. These genetic mutations include L861Q, G719X, and S768I mutations along with double-complex heterozygous mutations accompanying known drug-sensitive mutations (for example, L858R/T790M mutations). Dose modification recommendations for patients with certain CYP2D6 variants and liver impairment are unknown.
Conclusions	Gefitinib meets the criteria for traditional approval based on a favorable benefit–risk profile for the treatment of patients with metastatic *EGFR* mutation–positive NSCLC. Gefitinib demonstrated high and durable ORR in a single-arm trial, as well as supportive data suggesting a large magnitude of PFS benefit over conventional chemotherapy and improved tolerability in patients with *EGFR* mutation–positive NSCLC.

were diarrhea and rash (26). In addition to these adverse events, the IPASS study reported dry skin (24%; ref. 30), and the ISEL reported elevations in AST/ALT and proteinuria.

Currently, alongside erlotinib and afatinib, the approval of gefitinib represents a third option for patients with metastatic NSCLC harboring drug-sensitive *EGFR* mutations. Hence, patients and clinicians have a number of options to effectively treat this subtype of NSCLC with slightly varying adverse event profiles. Major unknown questions involve the use of gefitinib in tumors harboring rare *EGFR*-sensitizing mutation subtypes (e.g., G719X and L861Q). Given the rarity of these subtypes, they have been difficult to study, and the activity of gefitinib with these remains to be clarified. Patients with known acquired or intrinsic *EGFR* resistance mutations (T790M and exon 20 insertions) do not derive benefit from gefitinib treatment. Table 1 depicts the benefit–risk framework for gefitinib in the *EGFR* mutation–positive patient population.

Unfortunately, most patients invariably develop secondary drug resistance. Mechanisms of resistance not only involve gatekeeper mutations in *EGFR* (T790M), but also by a variety of other mechanisms. For example, Engelman and colleagues observed that in 4 of 18 lung cancer specimens, gefitinib resistance might develop through *MET* amplification and subsequent ERBB3-dependent activation of PI3K (31). Recently, resistance mechanisms have been grouped into four categories including (i) *EGFR* gatekeeper mutation (e.g., T790M), (ii) activation of a bypass signaling pathway (e.g., *MET* amplification), (iii) impairment of essential EGFR TKI–mediated apoptosis pathways, and (iv) histologic transformation to small cell lung cancer or an epithelial–mesenchymal transition (20, 32). Given this variation in resistance, determination of the mechanism in individual patients will be an essential strategy to overcome acquired resistance. For example, new drug development is focusing on next-generation irreversible selective EGFR inhibitors and concurrent use of MET inhibitors and other combination strategies. However, in addition to variation across patients, intrapatient tumor heterogeneity creates much complexity. In the future, a better understanding of resistance pathogenesis will be essential for drug development and successful long-term treatment of *EGFR*-mutated NSCLC.

The development of gefitinib in NSCLC is illustrative of a case where knowledge of the underlying biology of the cancer ultimately led to the appropriate evaluation of the drug in the right patient population, and serves as a great example of the evolution toward a more personalized approach to cancer therapeutics.

Authors' Contributions

Conception and design: D. Kazandjian, G.M. Blumenthal, R. Pazdur
Development of methodology: D. Kazandjian, G.M. Blumenthal, R. Pazdur
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Kazandjian, R. Pazdur
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Kazandjian, G.M. Blumenthal, W. Yuan, K. He, P. Keegan, R. Pazdur
Writing, review, and/or revision of the manuscript: D. Kazandjian, G.M. Blumenthal, W. Yuan, K. He, P. Keegan, R. Pazdur
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Pazdur

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