

# Approval reinstates gefitinib as a therapy for lung cancer

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This past summer, the United States joined more than 60 countries worldwide in approving the epidermal growth factor receptor (EGFR) inhibitor gefitinib for the treatment of patients with non-small-cell lung cancer (NSCLC) who harbor certain *EGFR* mutations. The approval marked “restoration of fortune” for the drug, which originally received accelerated approval from the US Food and Drug Administration (FDA) in 2003 for the treatment of advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel but was voluntarily withdrawn from the market after subsequent confirmatory randomized trials failed to verify a survival benefit.

The new approval is based on the multicenter, single-arm, phase IV IFUM trial,<sup>1</sup> a follow-up to the IPASS study,<sup>2</sup> upon which the 2009 approval of gefitinib in the European Union was partly based. The IFUM trial, which was carried out during September 2010-February 2012, was designed to address the fact that a relatively low number of non-Asian patients with *EGFR* mutations had been treated in the IPASS study.

Eligible patients were white, aged 18 years or older, and had a life expectancy of 12 or more weeks. They had histologically confirmed stage IIIA (if considered ineligible for curative therapy), IIIB, or IV NSCLC, with activating and sensitizing *EGFR* mutations (exon 19 deletions and exon 21 L858R mutations), a World Health Organization performance status of 0-2 (0, fully active; 2, ambulatory, capable of all self-care but unable to carry out any work activities), and were eligible for standard first-line therapy. Patients with *EGFR* mutations that were reported to confer resistance to EGFR tyrosine kinase inhibitors were not eligible.

Of the 1,060 patients screened from 13 countries, a total of 106 patients were enrolled and treated with oral gefitinib 250 mg once-daily, administered continuously until objective disease progression, intolerable toxicity, or discontinuation for another reason. Most of the patients were women (70.8%), had adenocarcinoma (97.2%), and were never-smokers (64.2%).

Tumor samples and duplicate plasma samples were collected at baseline for *EGFR* mutation testing and mutation status was determined using the theascreen EGFR RGQ\_PCR kit (Qiagen), an amplification refractory muta-

## What's new, what's important

Gefitinib has a unique historic role in the development of targeted therapies. Its rise and fall as a therapy in the United States in the early 2000s has taught us valuable lessons, especially about patient selection and enriching study populations in clinical trials. In particular, the pharmaceutical industry has shown some reluctance in identifying subsets of patients that would benefit from a treatment because of concerns that it would limit a product's market size.

Notable positive responses among some patients in early studies of gefitinib and other TKIs forced investigators to pay attention to and eventually identify the subset of patients who stood to benefit from the targeted therapy. Variation in responses among different patient populations – between races, men and women, smokers and nonsmokers – pushed us to continue to pay attention not just to the tumor heterogeneity, but to the heterogeneity of the patient population we care for.

In the end, patients with metastatic non-small-cell lung cancer who harbor certain EGFR mutations are the real winners. We now have one more drug with which to treat this serious disease, as well as a companion diagnostic assay for detecting whether a patient has the mutations.

The recommended dose of gefitinib is 250 mg orally once daily with or without food. Among the more common adverse effects associated with the therapy are rash, diarrhea, vomiting, and asthenia.

— Jame Abraham, MD, FACP (abrahamj5@ccf.org)

tion system (ARMS)-based *EGFR* mutation detection kit. Samples were considered positive when they had one or more activating, sensitizing *EGFR* mutations, with no ineligible mutations. The kit was also approved by the FDA as a companion diagnostic for gefitinib in this setting based on the results of this study, thereby expanding the indications for this diagnostic, which is already approved to guide the treatment of other EGFR-targeted therapies.

Tumor growth was assessed by a computed-tomography scan at 6-week intervals, and safety and tolerability was assessed continuously by adverse events (AEs) and clinical laboratory results. The primary endpoint was overall response rate (ORR), with secondary endpoints including progression-

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**Mechanism of action – gefitinib**  
**First-generation EGFR inhibitor blocks cancer hallmark pathway**

Receptor tyrosine kinases (RTKs) are a group of key cell surface receptors that are activated by growth factors, cytokines, and hormones, and possess intrinsic kinase activity – phosphorylating tyrosine residues on target proteins

and subsequently stimulating or inhibiting the activity of those proteins. The epidermal growth factor receptor (EGFR) is a member of the ErbB family of RTKs and is activated by a number of different ligands, including EGF. Among its target proteins are those involved in key intracellular signal transduction cascades, including the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways, which regulate central cellular processes such as proliferation.

Under normal conditions, activation of EGFR is tightly regulated by the availability of the ligand, but the pathway can become dysregulated by mutations in the receptor that lead to constitutive activation, even in the absence of ligand, promoting many of the hallmark abilities of cancer. Defects in the EGFR pathway have been implicated in a range of cancers, including NSCLC, in which *EGFR* mutations are found in around 10% of patients.

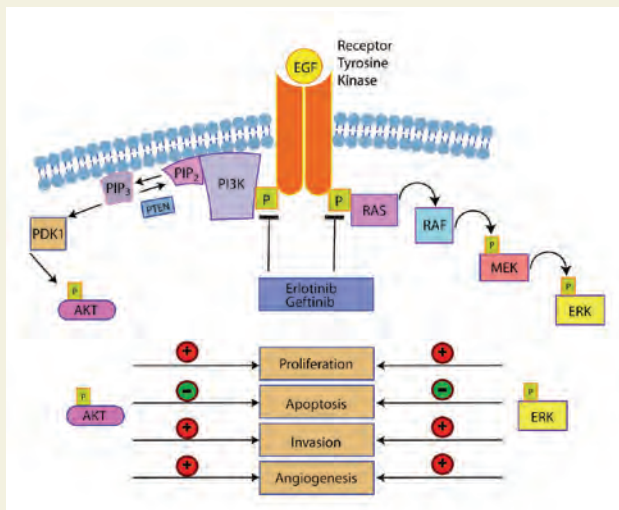
EGFR is one of the most comprehensively studied molecular targets in oncology and EGFR inhibitors have been under clinical

development for more than a decade. Gefitinib was the first EGFR-specific small molecule tyrosine kinase inhibitor to be developed. Though its antitumor mechanism of action is still not

fully understood, essentially it reversibly blocks the adenosine triphosphate-binding site of EGFR, blocking the kinase activity of both wild-type and certain mutant forms of EGFR. In doing so, it prevents autophosphorylation of tyrosine residues within the receptor, thereby suppressing its activation and inhibiting further downstream signaling mediated by the EGFR. It also inhibits other tyrosine kinases at clinically relevant concentrations, including insulin-like growth factor receptor.

Exon 19 deletions and exon 21 point mutations L858R in EGFR are the genetic alterations that are primarily responsible for inappropriate activation of its kinase activity. These mutations

also confer increased sensitivity to tyrosine kinase inhibitors like gefitinib. The turbulent history of gefitinib in clinical development demonstrates that clinical benefit is limited to patients with these specific mutations, while other mutations that confer resistance to EGFR inhibitors have also been identified. For this reason, gefitinib was approved in combination with a companion diagnostic assay that helps to identify the appropriate patient population.



Tyrosine kinase inhibitors such as gefitinib block the phosphorylation and activation of receptor tyrosine kinases, in this case EGFR, and prevent downstream signaling through PI3K and Ras pathways. This blocks the effects of activated EGFR on cancer hallmark processes including proliferation, apoptosis, invasion, and angiogenesis.

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free survival (PFS) and disease control rate (DCR), all determined by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

Over a median follow-up of 13 months, the ORR was 69.8% based on investigator assessment and 50% per secondary, supportive central review, and was consistent across subgroups. Response rates were similar in patients with both types of *EGFR* mutation. DCR was 90.6%, median PFS was 9.7 months, and median overall survival (OS) was 19.2 months. These results were supported by a retrospective analysis of a subgroup of 186 patients with *EGFR* mutation-positive, metastatic NSCLC who received first-line treatment in the IPASS trial. Eighty-eight of those patients received gefitinib 250 mg, and 98 received up to 6 cycles of chemotherapy. There was a 46% reduction in dis-

ease progression in the gefitinib group; median PFS was 10.9 months, compared with 7.4 months in the chemotherapy arm (hazard ratio, 0.54). ORR was 67%, compared with 41%, respectively, and duration of response was 9.6 months, compared with 5.5 months.

The median duration of exposure to gefitinib in the IFUM trial was 8 months, and 93.5% of patients experienced at least 1 AE during the study. The most common AEs were rash (44.9%), diarrhea (30.8%), vomiting (13.1%), asthenia, cough, and dry skin (all 11.2%), and nausea (10.3%). Serious AEs considered treatment-related occurred in 1.9% of patients. AEs led to treatment discontinuation in 7.5% of patients and death in 5 patients, as a result of cardiac failure, pneumonia, and Alzheimer-type dementia, none of which were considered related to gefi-

## How I treat patients with EGFR-mutant NSCLC

Analysis for the presence of EGFR activating mutation is standard practice for patients with advanced NSCLC. Mutations in the EGFR tyrosine kinase domain are observed in about 15% of NSCLC adenocarcinoma in the United States and occur more frequently in women and nonsmokers. In-frame deletions in exon 19 and the L858R point mutation in exon 21 are the 2 most common activating mutations. EGFR mutations significantly predict for both an increased response to TKI therapy and a favorable prognosis in patients with advanced lung adenocarcinoma. With the recent FDA approval of gefitinib, there are 3 drugs that are now approved for first-line therapy of patients with EGFR mutant NSCLC.

Erlotinib is preferred for use in the first-line setting based on familiarity of use and comfort level with management of side effects and toxicities. Afatinib, another TKI has also been approved for use in this setting and recent data demonstrated significantly prolonged overall survival in patients with exon 19 deletion compared with chemotherapy. The same advantage was not seen for patients with exon

21 mutations. With this recent data, afatinib has been the preferred agent for subset of patients exhibiting exon 19 deletions. Trials such as FLAURA and LUX-Lung 7 will help inform the selection of TKI agents in the front-line setting. Despite favorable response rates in the front line setting and impressive PFS duration, most patients with EGFR-mutant tumors sustain disease progression by 1 year, mostly owing to development of resistance by multiple disparate pathways. Repeat biopsy is recommended to look for T790M mutation, which accounts for 60% of all resistance mutations. Third-generation TKIs such as AZD 9291 and rociletinib are promising agents and are under consideration for expedited approval based on significant efficacy in patients with T790M mutant NSCLC. For patients without T790M mutations, other novel EGFR TKIs (TH 4000), combination approaches (such as cetuximab and afatinib) are being evaluated and clinical trial participation is encouraged. Chemotherapy remains a viable option for the second and third-line treatment for these patients.

— Charu Aggarwal, MD, MPH

tinib treatment. Pooled data from 2,462 patients enrolled in 3 randomized trials of gefitinib was used to evaluate serious and uncommon AEs. The most frequent fatal AEs were respiratory failure, pneumonia, and pulmonary embolism. The rate of discontinuation related to AEs was 5%, most commonly due to nausea, vomiting, and/or diarrhea.

The prescribing information details warnings and precautions on interstitial lung disease, hepatotoxicity, gastrointestinal perforation, severe or persistent diarrhea, ocular disorders, bullous and exfoliative skin disorders, and embryo-fetal toxicity.<sup>3</sup> Periodic liver function testing should be performed; pregnant women should be advised of the potential risk to the fetus, and women of reproductive potential should use contraception during treatment and for 2 months afterward. Concomitant use with proton pump inhibitors should be avoided, if possible, and patients using warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio.

Dose modifications in the case of AEs are also outlined. Gefitinib, which is marketed as Iressa by AstraZeneca, should be withheld for up to 14 days for acute onset or worsening pulmonary symptoms, grade  $\geq 2$  alanine aminotransferase or aspartate aminotransferase elevations, grade  $\geq 3$  diarrhea, grade  $\geq 3$  skin reactions, and signs and symp-

oms of severe or worsening ocular disorders, with treatment resuming when the AE fully resolves or improves to grade 1. Gefitinib should be permanently discontinued in the case of confirmed interstitial lung disease, severe hepatic impairment, gastrointestinal perforation, or persistent ulcerative colitis. The safety and efficacy of gefitinib has not been established in pediatric or geriatric patients or in those with renal impairment. AEs should be monitored in patients with moderate or severe hepatic impairment.

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