Report from the FDA

United States Food and Drug Administration Drug Approval Summary: Gefitinib (ZD1839; Iressa) Tablets

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Abstract

On May 5, 2003, gefitinib (Iressa; ZD1839) 250-mg tablets (AstraZeneca Inc.) received accelerated approval by the United States Food and Drug Administration as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies. Information provided in this summary includes chemistry manufacturing and controls, clinical pharmacology, and clinical trial efficacy and safety results. Gefitinib is an anilinoquinazoline compound with the chemical name 4-quinazolinamine,*N*-(3-chloro-4-flurophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]. It has the molecular formula $C_{22}H_{24}ClFN_4O_3$. Gefitinib is often referred to as a "specific" or "selective" inhibitor of epidermal growth factor receptor. Studies demonstrate, however, that gefitinib inhibits the activity of other intracellular transmembrane tyrosine-specific protein kinases at concentrations similar to those at which it inhibits the epidermal growth factor signal. Maximum plasma concentrations resulting from clinically relevant doses are 0.5–1 μM or more, well within the IC_{50} values of several tyrosine kinases. No clinical studies have been performed that demonstrate a correlation between epidermal growth factor receptor expression and response to gefitinib. Gefitinib is 60% available after oral administration and is widely distributed throughout the body. Gefitinib is extensively metabolized in the liver by cytochrome P450 3A4 enzyme. Over a 10-day period, approximately 86% of an orally administered radioactive dose is recovered in the feces, with <4% of the dose in the urine. After daily oral administration, steady-state plasma levels are reached in 10 days and are 2-fold higher than those achieved after single doses. Gefitinib effectiveness was demonstrated in a randomized, double-blind, Phase II, multicenter trial comparing two oral doses of gefitinib (250 *versus* 500 mg/day). A total of 216 patients were enrolled. The 142 patients who were refractory to or intolerant of a platinum and docetaxel comprised the evaluable population for the efficacy analysis. A partial tumor response occurred in 14% (9 of 66) of patients receiving 250 mg/day gefitinib and in 8% (6 of 76) of patients receiving 500 mg/day gefitinib. The overall objective response rate (RR) for both doses combined was 10.6% (15 of 142 patients; 95% confidence interval, 6.0–16.8%). Responses were more frequent in females and in nonsmokers. The median duration of response was 7.0 months (range, 4.6–18.6+ months). Other submitted data included the results of two large trials conducted in chemotherapy-naive, stage III and IV non-small cell lung cancer patients. Patients were randomized to receive gefitinib (250 or 500 mg daily) or placebo, in combination with either gemcitabine plus cisplatin ($n = 1093$) or carboplatin plus paclitaxel ($n = 1037$). Results from this study showed no benefit (RR, time to progression, or survival) from adding gefitinib to chemotherapy. Consequently, gefinitib is only recommended for use as monotherapy. Common adverse events associated with gefitinib treatment included diarrhea, rash, acne, dry skin, nausea, and vomiting. Interstitial lung disease has been observed in patients receiving gefitinib. Worldwide, the incidence of interstitial lung disease was about 1% (2% in the Japanese postmarketing experience and about 0.3% in a United States expanded access program). Approximately one-third of the cases have been fatal. Gefitinib was approved under accelerated approval regulations on the basis of a surrogate end point, RR. No controlled gefitinib trials, to date, demonstrate a clinical benefit, such as improvement in disease-related symptoms or increased survival. Accelerated approval regulations require the sponsor to conduct additional studies to verify that gefitinib therapy produces such benefit.

Introduction

Gefitinib (Iressa; ZD1839) is a member of a new class of oral drugs that inhibit receptor tyrosine kinases (TKs) including the epidermal growth factor receptor (EGFR)-TK; however, the precise anticancer mechanism of action has not been established. The submitted New Drug Application sought accelerated approval for gefitinib as monotherapy for patients receiving third-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC).

At present, four cisplatin-containing doublets (docetaxel, gemcitabine, paclitaxel, and vinorelbine) and single-agent vinorelbine are approved for the treatment of chemotherapy-naïve NSCLC patients. Docetaxel is approved for second-line therapy. Before gefitinib approval, third-line treatment was an unmet need.

This application received Fast Track designation (allowing early submission and review of application components) and

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priority review status (with a 6 month review goal). The final Chemistry, Manufacturing and Controls section of the New Drug Application was received on August 5, 2002. After safety reports of pulmonary toxicity became available from the Japanese post-marketing experience in October 2002, additional safety information was requested by the United States Food and Drug Administration. Supplemental information concerning interstitial lung disease (ILD) was provided in submissions through January 2003, resulting in an adjusted approval goal date of May 5, 2003.

Chemistry, Manufacturing, and Controls

Drug Substance. Gefitinib is an anilinoquinazoline compound with the chemical name 4-quinazolinamine,*N*-(3-chloro-4-flurophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]. The structural formula is represented in Fig. 1.

Gefitinib, a free base, has the molecular formula $C_{22}H_{24}ClFN_4O_3$. It is a white-colored powder. The molecule has pK_a values of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib is sparingly soluble at pH 1 and is practically insoluble above pH 7, with the solubility dropping sharply at pH 5.

The proposed drug substance specifications were found to be adequate, and the test data were acceptable. The drug substance is stored at controlled room temperature.

Drug Product. Iressa (gefitinib) film-coated tablets contain 250 mg of gefitinib/film-coated tablet. Twenty-four to 36 months of stability data from the supportive drug product stability batches were adequate to demonstrate the stability of drug product tablets under International Conference on Harmonization testing conditions.

No significant degradation in chemical and physical properties was observed in the drug product stability database. Based on these considerations, a drug product shelf life of 18 months was approved.

Nonclinical Studies

EGFR Background. EGFR was the first receptor protein recognized to be a tyrosine-specific protein kinase (1). Since that time, the number of receptor molecules identified as tyrosine-specific protein kinases has grown to include receptors for platelet-derived growth factor, insulin like growth factor I, fibroblast growth factor, vascular endothelial growth factor, and others. The names of these transmembrane receptor TKs are usually derived from the tissue from which they were first isolated. The name should not imply that those tissues are the only ones that express the receptor. The mechanisms of action for these receptor tyrosine-specific kinases have many similarities, and major portions of these proteins have considerable sequence homology (2, 3).

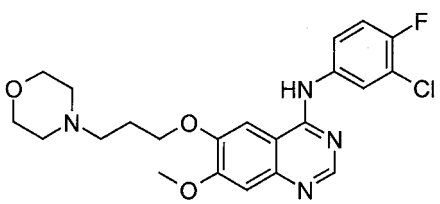

Fig. 1 Gefitinib structural formula.

Epidermal growth factor (EGF) binds to the extracellular domain of EGFR, a large single-pass transmembrane receptor protein. When two receptor proteins in close proximity bind EGF, an intracellular dimer is formed. The two components of the dimer autophosphorylate each other at multiple sites. This autophosphorylation step is essential for the initiation of kinase activity in most TK receptors proteins except EGFR, for which it is possibly only facilitative (4). A complex menagerie of intracellular signaling proteins then bind and are, in turn, phosphorylated (5). These proteins initiate a cascade of signals within the cellular cytoskeleton and the nucleus that regulate cell division. Other receptor TKs control cell division or other cell functions similarly. Cross-signaling among the downstream signaling proteins is considerable.

Many human tumors have high copy numbers of the EGFR and other receptor tyrosine-specific kinases on the cell surface. High copy number may result from overexpression at the transcription level or from a failure of the cell to attenuate the receptor signal by endocytosis (6). High copy number correlates with a poor clinical prognosis. Inhibition of EGFR dimerization by transfected dominant negative mutants of EGFR, blockade of EGFR expression with antisense nucleotides, or inhibition of the EGF signal with EGFR-specific antibodies can prevent EGF-stimulated cell division (7–9). These results led to the search for a small molecule EGFR inhibitor.

Gefitinib Mechanism of Action. Ward *et al.* (10) defined the kinetics of the ATP-driven phosphorylation of tyrosine by EGFR. They then selected likely inhibitors of EGFR based on structural similarities to ATP or tyrosine. The selected candidate drug was 4-(3-chloroanilino)-quinazoline. This compound competitively inhibited ATP in the reaction process with a much higher affinity for the ATP site than ATP itself (K_a/K_i = 390). Subsequently, Barker *et al.* (11) selected gefitinib as the most effective inhibitor of TK activity among a variety of substituted 4-(3-chloroanilino)-quinazolines. They further demonstrated that gefitinib was active against KB oral carcinoma cells *in vitro* and *in vivo*.

Many titles in the literature refer to gefitinib as a "specific" or "selective" inhibitor of EGFR. Nevertheless, few investigators have looked for interactions with other TK receptors. Gefitinib binds at the ATP site of the TK region, a region that is highly conserved across the various transmembrane TKs (11, 12). Table 1 shows *in vitro* cell type, the growth factor used to stimulate cell proliferation, and the IC_{50} of growth inhibition by gefitinib. The results suggest that gefitinib inhibits the activity of other intracellular transmembrane tyrosine-specific protein kinases at concentrations similar to those at which it inhibits the EGF signal. Maximum plasma concentrations resulting from clinically relevant doses are 0.5–1 μM or more, similar to or greater than many of these IC_{50} values. Therefore, gefitinib cytotoxicity could be the result of inhibition of downstream signal proteins or ATP-dependent kinases other than EGFR-TK.

Nonclinical Safety Studies. At physiological concentrations, gefitinib caused a dose-dependent prolongation of the Purkinje action potential of as much as 10 ms *in vitro*. This effect was not reversible after a 30-min washout period. Concentrations of about 1 μM *in vitro* also cause half-maximal

Table 1 IC_{50} of growth inhibition by gefitinib

Cells	Growth factor/stimulation	Gefitinib IC_{50} (μM)
HUVEC[a]	EGF	0.03–0.1
HUVEC	FGF	1–3
HUVEC	VEGF	1–3
NIH 3T3	PDGF	0.04
NIH 3T3	FGF	3.4
NIH 3T3	EGF	0.22
NIH 3T3	IGF	0.047
NIH 3T3	Lysophosphatidic acid	0.05

[a] HUVEC, human vascular endothelial cells; NIH 3T3, NIH 3T3 mouse fibroblasts; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor.

inhibition of the slow potassium rectifier. In dogs, at a dose of 1000 mg/m^2, gefitinib caused mild systolic and diastolic hypotension. The effect coincided with T_{max} and persisted for about 4 half-lives. The pressure drop caused a transient compensatory tachycardia followed by prolonged bradycardia. Thus, in dogs, gefitinib has significant effects on heart rate and blood pressure at doses less than 1 order of magnitude above the clinical dose. Potential mechanisms for this effect include interference with the slow potassium channel (IK_r), interference with cellular metabolism, or interference with angiotensin II signaling through its interaction with EGFR (13).

Gefitinib, by antagonizing ATP, may have the potential to interact with some of the numerous pharmacological sites that involve ATP. Such interaction at different sites may explain toxicities seen with chronic gefitinib dosing. Table 2 lists sites for which the inhibitory constant K_i is <5 μM.

Nonclinical Toxicology. In rats, single doses of gefitinib caused fatal toxicity at doses >80 times greater than the clinical daily dose (mg/m^2). Surviving rats recovered by day 15. Death was associated with microscopic damage in the adrenal glands, heart, liver, renal, kidneys, and spleen, suggesting causes unrelated to EGFR.

In multidose studies, dogs were more tolerant of gefitinib than rats. Dogs and humans show signs of clinically significant toxicity at about 300 mg/m^2/day. In all tested animal species, the difference between a chronic dose that caused relatively little toxicity and one that was lethal was <2-fold.

Animals that were given daily gefitinib for 2 weeks or longer showed signs of dose-dependent weight loss, alopecia, chronic active folliculitis, scabbing and tail lesions (rodents). Weight loss appeared to be related to loss of appetite and diarrhea.

Work by several groups suggest that gastrointestinal toxicities may be related to impairment of gastric epithelial repair mechanisms (14). Rats and dogs also demonstrated ocular toxicities including corneal atrophy, exudation and encrusting, reddened eyes, and swollen eyelids.

Organ weights of liver, lungs, spleen, thymus, and lymph nodes were increased. Macrophage infiltration, noted in the liver (centrilobular) and lung (bronchioles and interstitium), is consistent with inflammation and cell death in these tissues. Papillary renal necrosis, seen occasionally, may be related to interference with angiotensin II signaling at high gefitinib doses. The increase in the absolute and relative weight of the heart in rats appeared to be due to cardiac hypertrophy. In rats, microscopic liver damage was usually associated with 2- to 3-fold increases in serum alanine aminotransferase and aspartate aminotransferase and decreased serum albumin. Liver toxicity was less pronounced in dogs. Repeat dosing caused mild dose-dependent increase in WBC and platelet counts in both dogs and rodents.

Gefitinib was nonmutagenic in the Ames assay in the presence or absence of S9-mix. It did not increase the incidence of the micronucleated polychromatic erythrocytes in rats. Gefitinib was not genotoxic in an *in vitro* mouse lymphoma assay.

At doses that were toxic to the dams, gefitinib had no effect on female fertility when female rats were treated from 2 weeks before pairing through day 7 of gestation (segment I). Nevertheless, there was an increased incidence of irregular estrous cycles in rats given a 120-mg/m^2/day dose. This dose also caused significant embryo-fetal toxicity manifested as a decrease in corpora lutea, uterine implants, and live embryos per litter. Thus, gefitinib is an embryo-fetal toxin at doses approximately equivalent to the proposed clinical dose (mg/m^2). In rats, doses that caused dose-dependent maternal toxicity caused a dose-dependent decrease in fetal body weight. Gefitinib did not impair sperm function in male rats.

Clinical Pharmacology. After single-dose oral administration of gefitinib to cancer patients, peak plasma levels occurred within 3–7 h. Absolute bioavailability of gefitinib was 60%. A high-fat breakfast increased exposure to gefitinib [area under the curve (AUC)] by 30%. Interpatient variability of AUC was 45–70%. Gefitinib exhibits linear kinetics over the therapeutic dosing range. After a single 50-mg i.v. bolus dose, gefitinib is widely distributed throughout the body with a mean steady-state volume of distribution of 1400 liters. Mean total plasma clearance and elimination half-life of gefitinib were 595 ml/min and 48 h, respectively, after a single 50-mg i.v. bolus dose. After daily oral doses, steady-state plasma levels were reached in 10 days and were 2-fold higher than those achieved after single doses. About 90% of the radioactive orally administered dose was recovered in urine and feces over 10 days; 86% of dose was recovered in the feces, with <4% of the dose in the urine. The total binding of gefitinib to human plasma proteins was 91%. The binding proteins were serum albumin and α1-acid glycoprotein.

Gefitinib is extensively metabolized in the liver, predominantly by cytochrome P450 (CYP) 3A4. The identified meta-

Table 2 Pharmacological sites for which the gefitinib inhibitory constant K_i is less than 5 μM

	IC_{50} (μM)	K_i (μM)
Monoamine transporter	1.44	1.32
Dopamine D_{4-7}	3.39	3.6
Muscarinic, nonselective	4.4	1.45
Serotonin 5-HT_{26}	3.75	2.39
Sodium channel site 2	3.35	3
Sigma, nonselective	3.66	3.55
Adrenergic β_1	6.18	3.57
Serotonin 5-HT_{18}	6.16	3.77
Sigma σ_2	6.83	4.21
Dopamine transporter	5.33	4.23

bolic pathways include *O*-demethylation, dealkylation, and oxidative defluorination. The *O*-desmethyl derivative, the major metabolite identified in plasma, has exposure and EGFR-TK inhibition activity in an enzyme assay comparable with that of the parent drug (IC_{50} = 0.036 *versus* 0.033 μM, respectively).

Data were insufficient for definitive comparisons of pharmacokinetics among different racial and ethnic groups A cross-study comparison of Japanese and Caucasian patients showed comparable plasma exposure at similar gefitinib doses.

Pharmacokintec parameters were studied in patients with liver metastases and elevated serum liver tests (transaminase enzymes, alkaline phosphatase, and bilirubin). Patients received daily oral doses of 250 mg of gefitinib for 28 days. Patients with moderately and severely elevated liver tests had comparable gefitinib pharmacokinetics compared with individuals without liver abnormalities. No pharmacokinetic study has been conducted in renal impaired patients because <4% of gefitinib dose is excreted in the urine. No data are currently available on the pharmacokinetics of gefitinib in pediatric patients.

In vitro studies with human liver microsomes indicate that gefitinib has a weak inhibitory potential on CYP 1A2, CYP 2C9, and CYP 3A4 activities. Inhibition of CYP 2C19 and CYP 2D6 activity, however, is more pronounced (24% and 43%, respectively) at the highest gefitinib concentration (11.2 μM). These results indicate gefitinib may inhibit the metabolism of drugs that are substrates of CYP 2C19 and CYP 2D6. Gefitinib is a substrate of CYP 3A4. Concomitant administration of itraconazole, an inhibitor of CYP 3A4 enzyme, with gefitinib increased mean gefitinib AUC by 88%. Concomitant administration of rifampicin, an inducer of CYP 3A4 enzyme, reduced mean AUC of gefitinib by about 85%. Exposure to metoprolol, a substrate of CYP 2D6 enzyme, increased by 30% when given in combination with gefitinib. Concomitant administration of gefitinib with a high dose of ranitidine (to sustain the pH level above pH 5.0) decreased gefitinib AUC.

Clinical Studies

Third-Line NSCLC Treatment. The sponsor submitted two randomized, double-blind, Phase II, multicenter studies comparing two doses of gefitinib tablets (250 *versus* 500 mg/day). The first trial (for third-line treatment of advanced, metastatic NSCLC) provided the primary evidence supporting approval. Prior chemotherapy included a platinum drug and docetaxel given concurrently or sequentially. Study patients had disease progression within 90 days of their last treatment or treatment intolerance. The second trial (primarily patients receiving second-line treatment) enrolled patients who were recurrent or refractory to one or a maximum of two chemotherapy regimens, at least one of which had contained a platinum drug. This study provided additional evidence of gefitinib antitumor activity and safety.

A total of 216 patients at 30 United States medical centers were entered in the third-line treatment trial. Response rate (RR) and symptom improvement were co-primary efficacy end points. Of the 216 patients, 142 patients who had documented disease progression after platinum and docetaxel chemotherapy were evaluable for the primary analysis of RR and duration.

Patient demographics and disease characteristics of the evaluable treatment population are summarized in Table 3. Several findings were noted. Approximately 75% of evaluable study patients had adenocarcinoma histology (either alone or mixed with squamous cell histology). One-fourth of the patients had never smoked. The median time from lung cancer diagnosis to study randomization was 19.6 months.

Among the 142 evaluable patients, 15 partial responses (10.6%) were observed. The median response duration was 7 months (Table 4). Partial responses occurred in 9 of 66 patients receiving 250 mg/day gefitinib and in 6 of 76 patients receiving 500 mg/day gefitinib. The RR was similar in the 74 study patients who were not evaluable for the primary efficacy analysis (9.5%).

Exploratory analyses of RR in different subgroups of patients were performed (Table 5). Responding patients were predominantly female (11 of 15) and had adenocarcinoma (12 of 15). RRs did not appear to vary with performance status (0–1 *versus* 2) or number of prior therapies (2 *versus* 3 *versus* 4).

Whereas assessments of disease-related symptoms and quality of life were evaluated in both trials, conclusions may be questionable without comparison with a concurrent control group. Because there was no evidence of a gefitinib dose-

Table 3 Demographics and disease characteristics, third-line treatment population

Characteristic	Gefitinib dose	
	250 mg/day [n = 66 (%)]	500 mg/day [n = 76 (%)]
Age group (yrs)		
18–64	43 (65)	43 (57)
64–74	19 (29)	30 (39)
≥75	4 (6)	3 (4)
Sex		
Male	38 (58)	41 (54)
Female	28 (42)	35 (46)
Race		
White	61 (92)	68 (89)
Black	1 (2)	2 (3)
Asian/Oriental	1 (2)	2 (3)
Hispanic	0 (0)	3 (4)
Other	3 (5)	1 (1)
Smoking history		
Yes (previous or current smoker)	45 (68)	62 (82)
No (never smoked)	21 (32)	14 (18)
Baseline WHO performance status		
0	14 (21)	9 (12)
1	36 (55)	53 (70)
2	15 (23)	14 (18)
Not recorded	1 (2)	0 (0)
Tumor histology		
Squamous	9 (14)	11 (14)
Adenocarcinoma	47 (71)	50 (66)
Undifferentiated	6 (9)	4 (5)
Large Cell	1 (2)	2 (3)
Squamous & adenocarcinoma	3 (5)	7 (9)
Not recorded	0 (0)	2 (3)
Current disease status		
Locally advanced	11 (17)	5 (7)
Metastatic	55 (83)	71 (93)

Table 4 Response rate and response duration in third-line treatment of NSCLC[a]

	Evaluable patients		
	250 mg (n = 66)	500 mg (n = 76)	Combined (n = 142)
Objective response rate	13.6%	7.9%	10.6%
95% CI	6.4–24.3%	3.0–16.4%	6.0–16.8%
Median response duration			
Months	8.9	4.5	7.0
Range	4.6–18.6+	4.4–7.6	4.4–18.6+

+ = data are ongoing.
[a] NSCLC, non-small cell lung cancer; CI, confidence interval.

Table 5 Retrospective subgroup analyses of response rate in third-line treatment of NSCLC[a]

Subgroup	No. of patients in the subgroup	Response rate	95% CI
Females	63	17.5%	9.1–29.1%
Males	79	5.1%	1.4–12.5%
Nonsmokers	34	29.4%	14.6–46.3%
Smokers	108	4.6%	1.5–10.6%
Male smokers	65	3.1%	0.4–10.7%

[a] NSCLC, non-small cell lung cancer; CI, confidence interval.

response effect (250 and 500 mg/day gefitinib had comparable RRs), there was no valid comparator regimen allowing discrimination between observer bias and imatinib effect. Other methodologic issues included the use of concomitant medications that might have contributed to symptom relief. Both the United States Food and Drug Administration reviewers and the Oncologic Drugs Advisory Committee determined that the symptom and quality of life results could not be interpreted in this context. Therefore, quality of life and symptom results are not presented in this summary.

Second-Line NSCLC Treatment. A total of 210 patients (102 Japanese and 108 non-Japanese, predominantly Caucasian patients) who had previously received one or two prior chemotherapy regimens, at least one of which contained a platinum drug, were enrolled in this randomized Phase II trial. There were 39 patients with an objective tumor response.

Twenty-eight of the 102 Japanese patients (27.5%; 95% confidence interval, 19.1–37.2%) and 11 of the 108 non-Japanese patients (10.2%; 95% confidence interval, 5.2–17.5%) had tumor responses. In the combined group of Japanese and non-Japanese patients, 21 of the 62 female patients (33.9%; 95% confidence interval, 22.3–47.0%) and 18 of the 148 male patients (12.2%; 95% confidence interval, 7.4–18.5%) had tumor responses. Responding patients (35 of 39) predominantly had adenocarcinoma. The smoking history in these patients was not available.

First-Line NSCLC Treatment in Combination with Chemotherapy. Two large trials were conducted in chemotherapy-naïve, stage III and IV NSCLC patients. A total of 2130 patients were randomized to receive gefitinib (250 or 500 mg daily) or placebo in combination with platinum-based chemotherapy regimens. The chemotherapy regimens in these first-line trials were gemcitabine plus cisplatin ($n = 1093$) or carboplatin plus paclitaxel ($n = 1037$). Results from these studies showed no benefit (RR, time to progression, or survival) from adding gefitinib to chemotherapy (Table 6).

Safety. Drug-related adverse events occurring with an incidence of ≥5% in either the 250- or 500-mg dose group are summarized in Table 7. The most common adverse reactions were diarrhea, rash, and acne. Treatment-related delays and dose reductions occurred more often in the 500 mg/day dose group than in the 250 mg/day dose group (dose delays, 26% and 15%, respectively; dose reductions, 10% and 1%, respectively). Most toxicities were grade 1 or 2 (Common Toxicity Criteria).

Asymptomatic increases in liver transaminases have been observed in gefitinib-treated patients; therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) should be performed. Discontinuation of gefitinib should be considered if changes are severe.

Pulmonary Toxicity. Cases of ILD have been observed in patients receiving gefitinib. ILD is a complex disease, described by investigators using different terms (the sponsor captured cases by a collection of 24 Medical Dictionary for Regulatory Affairs terms). The United States Food and Drug Administration performed a detailed analysis of the sponsor drug safety database. This included 50,005 patients (including 18,960 from marketed use in Japan). A total of 408 cases of ILD (324 from Japan and 84 from the United States/rest of the world) were identified. Median time to onset of ILD was 24 days in Japan and 42 days in the United States experience. Worldwide, the incidence of ILD associated with gefitinib treatment was about 1% (2% in the Japanese post-marketing experience and about 0.3% in approximately 23,000 patients treated with ge-

Table 6 Phase III first-line efficacy results

Treatment arm	n	% Response rate (95% CI)[a]	Median progression-free survival (days) (95% CI)	Median survival (days) (95% CI)	*P* (survival)
Gemcitabine + cisplatin +					
250 mg gefitinib	365	50.1 (44.7–55.6)	178 (153–190)	299 (255–325)	0.4832
500 mg gefitinib	365	49.7 (44.2–55.2)	169 (144–187)	268 (242–316)	0.3041
Placebo	363	44.8 (39.3–50.4)	182 (166–188)	302 (272–342)	
Paclitaxel + carboplatin +					
250 mg gefitinib	347	35.0 (29.6–40.6)	162 (133–175)	300 (264–334)	0.6429
500 mg gefitinib	345	32.1 (27.0–37.7)	142 (127–160)	302 (268–352)	0.6710
Placebo	345	33.6 (28.1–39.3)	154 (132–176)	337 (307–368)	

[a] CI, confidence interval.

Table 7 Drug-related adverse events with an incidence of ≥5%

Drug-related adverse event[a]	250 mg/day (n = 102) (%)	500 mg/day (n = 114) (%)
Diarrhea	49 (48)	76 (67)
Rash	44 (43)	61 (54)
Acne	25 (25)	37 (33)
Dry skin	13 (13)	30 (26)
Nausea	13 (13)	20 (18)
Vomiting	12 (12)	10 (9)
Pruritus	8 (8)	10 (9)
Anorexia	7 (7)	11 (10)
Asthenia	6 (6)	5 (4)
Weight loss	3 (3)	6 (5)

[a] A patient may have had more than one drug-related adverse event.

fitinib in a United States expanded access program). In the randomized studies of gefitinib combined with chemotherapy, the ILD rate was about 1%, and the rate was similar in the gefitinib and control (chemotherapy plus placebo) arms. Approximately one-third of all ILD cases have been fatal. Patients often present with the acute onset of dyspnea, with or without cough or low-grade fever. Symptoms often become severe within a short time and require hospitalization.

ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported cases), and no previous therapy. Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving gefitinib have been observed to have an increased rate of mortality.

In the event of pulmonary symptoms (dyspnea, cough, and fever), gefitinib therapy should be interrupted, and a prompt investigation of these symptoms should occur. If ILD is confirmed, gefitinib should be discontinued, and the patient should be treated appropriately.

Conclusions

The accelerated approval regulations allow approval of cancer drugs based on a surrogate end point when the drug provides benefit over available therapy. Gefitinib received accelerated approval based on an objective RR of 10.6% with a median response duration of 7 months in the third-line treatment of NSCLC, a setting where no drug has demonstrated efficacy. Under the accelerated approval regulations, the sponsor will be required to conduct additional studies to verify that gefitinib therapy is associated with clinical benefit in NSCLC. The sponsor has committed to perform the following randomized trials:

(*a*) A double-blind Phase III trial comparing survival of gefitinib plus best supportive care *versus* placebo plus best supportive care in advanced NSCLC patients who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

(*b*) A double-blind Phase III trial evaluating RR, time to progression, survival, and symptom improvement of gefitinib *versus* docetaxel in advanced NSCLC patients who have received first-line treatment and have recurrent or progressive disease.

(*c*) A double-blind Phase III trial evaluating symptom improvement of gefitinib plus best supportive care *versus* placebo plus best supportive care in symptomatic advanced NSCLC patients who have received one or two prior regimens and are refractory or intolerant to their most recent regimen.

The following ongoing trials are not a requirement of the accelerated approval but will also be completed:

(*a*) A Phase III double-blind, placebo-controlled trial of gefitinib adjuvant treatment in completely resected stage I, II, and IIIA NSCLC patients. This trial is being conducted by National Cancer Institute-Canada and the European Organization for Research and Treatment of Cancer.

(*b*) A double blind, placebo-controlled trial of cisplatin/etoposide/radiotherapy with consolidation docetaxel followed by maintenance therapy with gefitinib or placebo in patients with inoperable Stage III NSCLC. This trial is being conducted by Southwest Oncology Group.

On May 5, 2003, gefitinib 250-mg tablets received accelerated approval by the United States Food and Drug Administration as monotherapy treatment for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The recommended gefitinib dose is 250 mg/day because the 500-mg/day dose was more toxic and no more effective.

The effectiveness of gefitinib is based on objective RRs. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Results from two large, controlled, randomized trials showed no benefit from adding gefitinib to doublet, platinum-based chemotherapy in first-line treatment of NSCLC. Therefore, gefitinib is not indicated for use in this setting.

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