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RESEARCH**

APPLICATION NUMBER:

206995Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 4, 2015
From	Gideon M. Blumenthal, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206995
Supplement#	
Applicant	Astra Zeneca Pharmaceuticals LP
Date of Submission	September 17, 2014
PDUFA Goal Date	July 17, 2015
Proprietary Name / Established (USAN) names	Iressa (Gefitinib)
Dosage forms / Strength	tablets, 250 mg
Proposed Indication(s)	For the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
Recommended:	<i>Approval</i>

Discipline and Consultants	Primary/ Secondary Reviewer
Clinical Review	Dickran Kazandjian, M.D./ Gideon Blumenthal, M.D.
Statistical Review	Weishi Yuan, Ph.D./ Kun He, Ph.D.
Regulatory Project Manager	Sharon Sickafuse
Pharmacology Toxicology Review	Sachia Khasar, Ph.D./ Whitney Helms, Ph.D.
CMC and Biopharmaceutic Reviews	Product: Donghao (Robert) Lu, Ph.D./ Olen Stephens, Ph.D. Biopharm: Salahelding Hamed, Ph.D./ Okpo Eradiri, Ph.D., Microbiology: Robert Mello, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Robert Schuck, Ph.D./ Hong Zhao, Ph.D. Pharmacometrics: Jerry Yu, Ph.D./ Liang Zhao, Ph.D./ Yaning Wang, Ph.D. Genomics: Rosane Charlab Orbach, Ph.D. QT-IRT: Dinko Rekiec
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Facility Inspection Review (OC/OMPQ/DGMPA)	Robert Wittorf, PharmD
CDRH	Jennifer Shen, Ph.D./ Reena Philip, Ph.D.

1. Introduction

On September 7, 2014, Astra Zeneca (Applicant) submitted New Drug Application (NDA) 206995 for gefitinib (Iressa). The Applicant proposed the following indication: for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Gefitinib is an oral, reversible, EGFR tyrosine kinase inhibitor (TKI). The U.S. FDA previously granted gefitinib accelerated approval under 21 CFR 314, subpart H in May 2003 under NDA 21399 for the treatment of unselected patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel. Following the failure to confirm clinical benefit in three post marketing studies, the Applicant voluntarily withdrew NDA 21399 for marketing in the U.S. in April 2012.

In December 2013, IND 120992 was opened with a request for a pre-NDA meeting to discuss a new NDA for gefitinib for patients with metastatic NSCLC whose tumors harbored EGFR sensitizing mutations. In March 2014, a Type B pre-NDA meeting was held to discuss the content and format of the NDA. As agreed, the primary basis for the NDA is the results from the Iressa Follow-up Measure Study (heretofore named IFUM), an open-label, multicenter, single arm study of gefitinib 250 mg as first line treatment in patients with EGFR mutation-positive metastatic NSCLC conducted in Caucasian patients in Europe. The primary efficacy data to support the single arm IFUM study is a retrospective subset analysis of patients with EGFR mutations in IPASS, an open label, randomized, multicenter, phase 3 study of gefitinib versus carboplatin/paclitaxel doublet chemotherapy in clinically selected patients with metastatic NSCLC in Asia. Also supportive of efficacy were a literature review of two randomized Japanese studies, WJTOG3405 and NEJ002, prospectively comparing gefitinib with platinum doublet chemotherapy in patients with EGFR mutation positive metastatic NSCLC.

To assess the safety of gefitinib, common side effects over background was assessed in the Iressa survival evaluation in lung cancer (ISEL), a double-blind, placebo-controlled randomized study of 2nd and 3rd line treatment of patients with unselected metastatic NSCLC. To characterize uncommon adverse reactions, the safety databases of ISEL and IPASS were pooled with the study “Iressa NSCLC trial evaluating response and survival versus Taxotere” (INTEREST) in patients with second line metastatic NSCLC.

2. Background

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined. Estimated new lung cancer cases for 2014 are 224,210, contributing to 159,260 deaths. Non-small cell lung

cancer (NSCLC) accounts for approximately 85% of lung cancer cases, with an expected 5-year survival of 1-5% for advanced disease. In unselected patients, cytotoxic platinum doublet based chemotherapy is the backbone of first-line treatment for patients with metastatic disease, with median survivals ranging from 8 to 12 months. In the second-line treatment setting of unselected patients with advanced NSCLC, docetaxel (with or without ramucirumab), pemetrexed (non-squamous), and erlotinib are FDA-approved.

Starting in 2004, with improved genomic sequencing technology, somatic mutations in the kinase domain of EGFR were found to be a relatively frequent oncogenic driver in patients with metastatic NSCLC of adenocarcinoma histology. EGFR mutations are more common in East Asian patients, females, and those who never smoked. The incidence of EGFR mutations in the U.S. Adenocarcinoma NSCLC patient population is roughly 20%.

Gefitinib was initially developed in the era before widespread genomic screening for oncogenic driver mutations. Gefitinib initially received accelerated approval in 2003 based on a 15% ORR in a single arm trial in an unselected patient population (likely those who responded had undetected EGFR mutations). As a condition of accelerated approval, the Applicant was required to perform post-marketing confirmatory studies, all of which were performed in unselected patient populations, and all of which failed to confirm clinical benefit. The Applicant voluntarily withdrew gefitinib from the U.S. market in 2012. In 2013, the U.S. expanded the indication for another EGFR TKI, erlotinib (Tarceva) for the first line treatment of patients with metastatic NSCLC whose tumors harbor exon 19 deletions and exon 21 L858R substitution mutations as detected by an FDA approved test, and approved an irreversible EGFR TKI afatinib (Gilotrif) for this same indication. The Applicant submitted a new NDA for gefitinib for this narrower, biomarker-enriched population of patients with somatic activating and sensitizing EGFR kinase domain mutations.

3. CMC/Device

- Device (in vitro diagnostic):

The Applicant is collaborating with Qiagen to provide a companion diagnostic to support the proposed indication. Qiagen has submitted a contemporaneous PMA supplement for the theascreen® EGFR RGQ PCR Kit (EGFR Kit) as a companion diagnostic. The PMA supplement is currently under review by CDRH OIR OIVD. Per the CDRH review team, the sPMA appears to be on schedule for contemporaneous approval with the NDA.

- General product quality considerations
Drug Substance: The drug substance is Gefitinib. It is a free base. The chemical name is N-(3-chloro-4-fluorophenyl-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine. It has a molecular formula of C₂₂H₂₄ClFN₄O₃ and its molecular weight is 446.90. The drug substance specification includes: description, identification, assay, impurities, residual solvents, (b) (4) water content, and particle size distribution. The drug substance is physically and chemically stable based on evaluation of the testing data.

Drug Product: The drug product is IRESSA (gefitinib) tablets containing 250 mg of gefitinib and is available as brown film-coated tablets. It is intended for oral administration.

IRESSA 250 mg tablets are packed in square, white, 75 ml, high-density polyethylene (HDPE) bottles with (b) (4) cap. Inside the cap is a (b) (4). Each bottle contains 30 tablets. The drug substance has a retest period of (b) (4).

The inactive ingredients of IRESSA tablets consist of: (1) Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate; (2) Coating: hydroxypropyl methylcellulose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide. The drug product is physically and chemically stable based on evaluation of the testing data. The drug product has a shelf life of 48 months. The drug product should be stored at controlled room temperature 20-25 degrees C (68-75 degrees F).

Biopharmaceuticals: Per Biopharmaceutics, the dissolution method and acceptance criterion NDA 206995 for IRESSA, Gefitinib 250 mg film-coated tablets are acceptable. The Division of Biopharmaceutics therefore recommends approval of NDA 206995 for Iressa tablets, 250 mg.

The dissolution methods and acceptance criterion, agreed to with the Applicant, and to be implemented for Iressa Tablets, 250 mg are summarized as follows:

Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP Apparatus 2/ 50 rpm	5% v/v Tween 80 in Water	1000 mL	Q = (b) (4)% at 45 min

- Product Quality Microbiology: Acceptable per NDA 21-399
- Facilities review/inspection: Approve (per Robert Wittorf, May 12, 2015)
- Other notable issues (resolved or outstanding): None

Overall CMC recommendation [Donghao (Robert) Lu, Ph.D. and Olen Stephens, Ph.D., 5/12/15]: From a CMC perspective, AstraZeneca has submitted sufficient and appropriate information to support the approval of the drug product. Iressa (gefitinib) 250 mg tablets was approved for marketing with NDA 21-399 on May 5, 2003, for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The NDA 21-399 was voluntarily withdrawn on April 25, 2012. AstraZeneca submitted an IND amendment to Iressa pre-IND 120,992 on May 7, 2014 (Sequence 0007), describing the differences in CMC and facilities between NDA 21-399 and this NDA 206-995. Based on the evaluation, the drug product Iressa tablets, 250 mg, is recommended as APPROVAL from a CMC perspective.

During the review, risk-based approaches have been used to assess the product development, manufacturing process and quality control. As this is a previously approved drug product, the review focuses on the differences between the two NDAs (including the NDA 21-399 supplements).

4. Nonclinical Pharmacology/Toxicology

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise):

The Applicant provided data from the scientific literature suggesting that certain EGFR kinase domain mutations (such as exon 19 deletion and exon 21 L858R substitution) leads to EGF- activation which is enhanced and prolonged compared to wild-type EGFR. Gefitinib inhibited EGF-induced auto-phosphorylation of mutant receptors ($IC_{50}=15nM$) at lower concentrations than wild-type receptors ($IC_{50}=100nM$). The data also demonstrated that inhibition of L858R EGFR phosphorylation inhibited downstream targets ERK1/2 and AKT.

In vivo data using NCI-H3255 L858R or the PC9 Ex19del cell lines in mouse xenograft models showed gefitinib-mediated inhibition of tumor growth and tumor regression. Data previously reviewed under NDA 21,399 showed that tumor volume growth was inhibited but did not regress when treated with gefitinib in A549-bearing nude mice (EGFR wild-type). Thus, in vivo data support the in vitro findings of higher sensitivity to gefitinib in tumors with selected EGFR mutations.

- Carcinogenesis, Mutagenesis

Gefitinib was not genotoxic in a series of in vitro (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an in vitro rat micronucleus test.

In a two-year carcinogenicity study in mice, administration of gefitinib at a dose of 270 mg/m²/day (approximately twice the recommended human dose) caused hepatocellular adenomas in females. In two-year carcinogenicity studies in rats, administration of gefitinib at 60 mg/m²/day (approximately 0.4 times the recommended daily clinical dose) caused hepatocellular adenomas and hemangiomas plus hemangiosarcomas of the mesenteric lymph nodes in female rates.

- Reproductive toxicology and fertility

A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m², about 0.2 times the recommended human dose). When pregnant rates were treated with ≥ 5 mg/kg from the beginning of organogenesis to the end of weaning, there was a reduction in the number of offspring born alive. The effect was more severe at 20 mg/kg (approximately the human dose) and was accompanied by high neonatal mortality. In rabbits, a dose of 20 mg/kg/day (240 mg/m², about twice the recommended human dose) caused reduced fetal weight. Therefore, the Pharmacology/Toxicology team recommended Pregnancy Category D.

In a dedicated fertility study in rates at doses ≥ 120 mg/m² (about equal to the human dose), animals presented with an increased incidence of irregular estrous, decreased corpora lutea, and decreases in uterine implants and live embryos per litter.

Overall Recommendation [G. Sachia Khasar, Ph.D. and Whitney S. Helms, Ph.D., 5/12/15]: There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of gefitinib for the treatment of patients with ^{(b) (4)} metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R ^{(b) (4)} substitution mutations as detected by an FDA-approved test.

5. Clinical Pharmacology

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

According to the Applicant, the permeability and absorption data support a Biopharmaceutical Classification System (BCS) category of Low Solubility-High Permeability (Class II). In cancer patients, the absolute bioavailability of gefitinib is 59%. The proposed labeling recommends dosing with or without food, consistent with the IFUM and IPASS studies.

The relative bioavailability of gefitinib when administered as a dissolved tablet preparation (in a drink or via nasogastric tube) compared to the tablet formulation was evaluated in healthy male subjects. AUC and C_{max} were similar following

administration of the tablet dispersion via drink or nasogastric tube. Instructions on how to prepare and administer the dissolved tablet are included in proposed labeling for patients who have difficulty swallowing solids.

Gefitinib has a Tmax of 3 to 5 hours and the mean single-dose terminal half-life is about 41 hours. The steady state apparent volume of distribution is 1400L, suggesting that it is extensively distributed into tissues. Plasma protein binding is about 91%, independent of concentration over the range of 50 to 8000 ng/ml. When administered to healthy volunteers under fed conditions, AUC increased by 37% and Cmax by 32% compared to that under fasting conditions. In cancer patients, gefitinib exhibits linear PK over the oral dose range of 50 to 400 mg daily, and non-linear PK over the dose range of 50 to 700 mg daily. Following chronic daily dosing, steady state plasma concentrations are approximately 2-fold higher than those observed after single-dose administration in both patients and healthy subjects.

Gefitinib PK is highly variable in both healthy individuals and patients, with AUC values typically covering a 20-fold and 8-fold range, respectively. In a dedicated study of healthy male subjects to assess intra-subject variability, the intra-subject range was up to 2-fold for AUC and up to 3-fold for Cmax, however the half-life appeared consistent within each subject. In the same study, the inter-subject variability for AUC was 66-67% for AUC and 52-55% for Cmax.

- Drug-drug interactions and Pathway of elimination

Drug-drug interactions:

Victim: Gefitinib is extensively metabolized, and cytochrome P450 (CYP) 3A4 is the major enzyme contributing to metabolism of the parent drug. However, the major metabolite (M523595), which is present in plasma at similar concentrations as gefitinib, is produced exclusively through metabolism of gefitinib by CYP2D6.

In vivo drug interaction studies demonstrated that the strong CYP3A4 inhibitor itraconazole increased gefitinib AUC by 80% and Cmax by 51% (following a 250 mg oral dose of gefitinib). No dose adjustment is recommended with co-administration of a strong CYP3A4 inhibitor based on the low dose reduction rates (1-10%) at 250 mg and 500 mg observed in clinical trials. The strong CYP3A4 inducer rifampicin decreased gefitinib AUC by 83% and Cmax by 65% (following a 250 mg oral dose of gefitinib). The proposed labeling recommends consideration of a dose increase to 500 mg daily when administered with a strong CYP3A4 inducer. Increased gastric pH (maintained at >5 with ranitidine (b) (4) sodium bicarbonate if needed) reduced AUC by 47% (b) (4). FDA recommends avoiding proton pump inhibitors, if possible, and scheduling modifications when taking gefitinib with H2 antagonists or antacids concurrently.

A bi-directional permeability study indicates that gefitinib is a P-gp substrate but not an inhibitor.

Perpetrator: In vitro studies suggest that gefitinib may inhibit the metabolism of drugs that are substrates of CYP2C19 and CYP 2D6. In an open-label study of 18 cancer patients, the AUC of metoprolol increased 35% with co-administration of gefitinib.

Pathway of elimination: Following oral administration of 250 mg [¹⁴C] gefitinib, 81% of radioactivity was recovered in feces and 4% in urine. Only 4% of the dose recovered in feces was unchanged gefitinib, indicating that gefitinib is extensively metabolized in humans. In vitro studies suggest that gefitinib is predominantly metabolized by CYP3A4 and CYP2D6 with CYP3A5 also contributing. The levels of radioactivity detected in plasma were very low.

- Intrinsic and extrinsic factors

Intrinsic factors:

Age, race, body weight: In clinical studies of gefitinib, age, race and body weight did not appear to affect exposure. Caucasian female patients tend to have higher exposures (~27%) to gefitinib compared to Caucasian male patients following a single 250 mg oral dose.

Hepatic Impairment: Based on a study of patients with hepatic impairment due to cirrhosis, exposure to gefitinib is approximately 1.4-, 3.6-, and 2.7- fold higher in subjects with mild, moderate, and severe hepatic impairment. The PK of gefitinib in patients with hepatic impairment due to cirrhosis is highly variable, inconsistent with the degree of impairment, and exposures in each group overlapped. Considering the low dose reduction rate observed when gefitinib was administered at 2-fold higher than the recommended dose, no specific dose adjustment is recommended in patients with moderate and severe hepatic impairment. In a separate study in cancer patients with hepatic impairment secondary to liver metastases, gefitinib exposures were similar in patients with moderate and severe impairment due to liver metastases compared to patients with normal hepatic function.

Pharmacogenomics: Subjects who are CYP2D6 poor metabolizers (PM) have approximately 2-fold higher exposure to gefitinib than CYP2D6 extensive metabolizers (EM). However, the PK of gefitinib is highly variable, and exposures in each group overlapped. Based on the low dose reduction rate when gefitinib was administered at 2-fold higher dose, no specific dose adjustment is recommended in CYP2D6 PMs. It is unknown whether patients who are CYP2D6 ultra metabolizers (UM) would benefit from a higher dose of gefitinib. The clinical pharmacology team recommended that further investigation is warranted, however this did not rise to the level of a post-marketing commitment, and submitted the recommendation to the IND. I concur with this assessment.

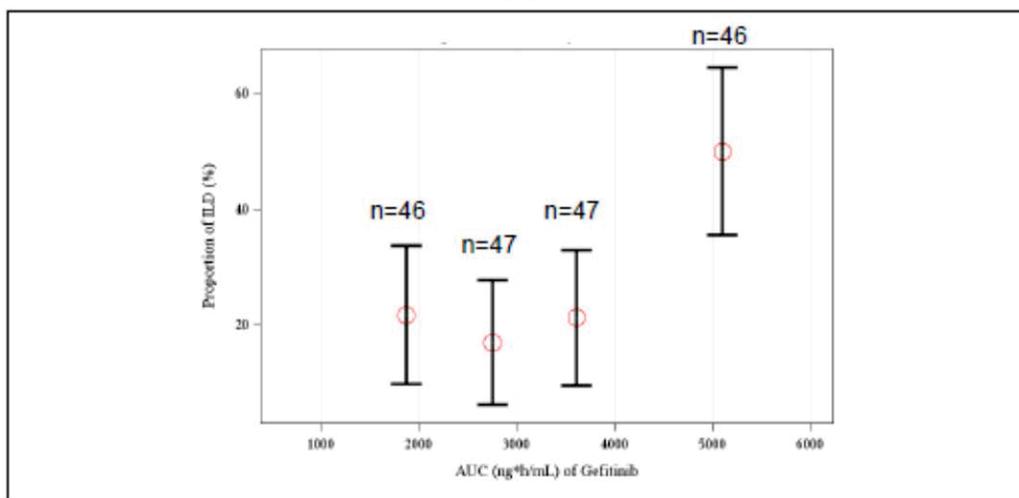
Extrinsic factors: see DDI discussion above.

- Exposure-Response:

The E-R relationship for response rate in the IFUM study (n=103) is flat across C_{min} quartiles.

- **Exposure-Safety**
The most common drug related AEs observed in phase 1 studies were skin and gastrointestinal toxicities, which were dose related. In phase 2 studies, AEs increased in frequency and severity with the 500 mg daily dose. An apparent association between exposure and ILD was identified based on an observational study (study code: V-15-33) where sparse PK samples were collected in Japanese patients with advanced NSCLC who developed ILD (n=186) and compared to randomly selected patients without ILD. This exploratory analysis showed an apparent association between exposure and ILD in that the highest exposure quartile appeared to have a 2-fold higher incidence of ILD.

Exploratory nested retrospective Exposure-Safety study of ILD in Japanese patients with advanced NSCLC taking gefitinib



In the IFUM study, there was no apparent Exposure-Safety relationship with respect to rash across C_{min} quartiles but there was an apparent E-S relationship with respect to diarrhea.

Despite the apparent E-S relationship for ILD and diarrhea, the clinical pharmacology team recommended no dose adjustment in patients with moderate or severe hepatic impairment (HI) due to cirrhosis. The PK profiles of 250 mg every other day was evaluated in severe HI patients by PK simulations based on the findings in a dedicated clinical pharmacology study. These simulations indicated that the median concentration in normal subjects and patients with severe HI due to cirrhosis are comparable. However, the lower bound (i.e. 5 percentile) of trough concentrations in patients with HI following 250 mg QOD are 27% lower than those in normal subjects following 250 mg QD, largely due to higher variability observed in patients with severe HI (CV% of AUC: 104% in patients with severe hepatic impairment vs. 81% in normal subjects). This result suggests a potential loss of efficacy in such patients with dose adjustment. Given the potential loss of efficacy with dose reduction and

acceptable safety profile 500 mg QD observed in clinical studies, no dose adjustment is recommended in patients with hepatic impairment or CYP2D6 PMs.

- QT assessment:
No thorough QT (TQT) study was conducted to evaluate the effect of gefitinib on the QT interval. The relationship between gefitinib concentration and QT was assessed using data collected from study D4200C000003, a randomized double-blind, 2-part, multicenter study comparing the efficacy of ZD6474 with gefitinib in patients with mNSCLC. The study report was evaluated by the QT-IRT team. According to QT-IRT, no large change (i.e., >20 ms) in the QTcF interval was detected when multiple doses of 250 mg gefitinib were administered.

Overall Recommendation from Clinical Pharmacology (5/12/2015): The NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA. There is no post-marketing requirement (PMR) or post-marketing commitment (PMC) study recommended at this time.

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 3 for product quality microbiology information.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the statistical reviewer (Dr. Weishi Yuan) and clinical reviewer (Dr. Dickran Kazandjian) regarding the efficacy of gefitinib for patients with EGFR-mutation positive (sensitizing and activating) metastatic NSCLC.

The following summarizes the key milestones in the regulatory history.

- November 1997: IND 54,576 opened
- May 2003: gefitinib granted accelerated approval under 21 CFR 314 for treatment of unselected patients with locally advanced or metastatic NSCLC after progression of platinum-based and docetaxel chemotherapies
- June 2005: indication restricted to use in only those patients already receiving and benefiting from gefitinib after failure to confirm clinical benefit in post-marketing studies in unselected metastatic NSCLC patients (IBREESE, ISEL, INTEREST)
- September 2011: gefitinib NDA voluntarily withdrawn (published in Federal Register April 2012)

- December 2013: pre-IND opened for first-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have EGFR Exon 19 deletions or Exon 21 substitution L858R mutations as detected by an FDA-approved test.
- March 2014: pre-NDA meeting held
- September 2014: NDA submission

Efficacy Summary:

IFUM

The primary efficacy analysis of gefitinib for the first-line treatment of patients with metastatic NSCLC containing EGFR activating and sensitizing mutations was derived from IFUM (D791AC00014), a multicenter, single, arm, open-label study conducted in Europe. In the final IFUM study protocol, a total of 100 patients were expected to be enrolled (after an expected screening of 1250 Caucasian patients). The applicant did not perform a power analysis for sample size calculations.

After screening a total of 1060 patients, a total of 106 treatment-naïve patients with metastatic EGFR mutation positive NSCLC received at least one dose of gefitinib at 250 mg once daily until progression or intolerable toxicity. These 106 patients comprise the Full Analysis Set (FAS) population. Five patients enrolled but were not included in the FAS, four did not receive at least one dose of gefitinib (one due to AE, 3 due to not meeting eligibility) and one patient erroneously received gefitinib for 22 days but should have been excluded due as she had an exon 20 insertion mutation in EGFR.

The major efficacy outcome was objective response rate (ORR) according to RECIST v1.1 as evaluated by both investigators and a Blinded Independent Central Review (BIRC). Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L861Q, or G719X substitution mutation and no T790M or S681 mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. The Applicant retrospectively tested tumor samples from 84 patients using the *therascreen* EGFR RGQ PCR kit.

The study population characteristics were: median age 65 years, age 75 years or older (25%), white (100%), female (71%), never smokers (64%), WHO PS 0-1 (93%), adenocarcinoma histology (96%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitutions (31%), while two patients each had tumors harboring L861Q or G719X.

The ORR and DOR is presented in the following table. Of note, 17 patients were deemed not to have target lesions at baseline by the BICR and were deemed non-responders.

ORR and DOR in patients with EGFRm+ NSCLC treated with gefitinib in IFUM

Efficacy Parameter	Investigator Assessment (N=106)	BIRC Assessment (N=106)
ORR (95% CI)	70% (60, 78)	50% (40, 60)
CR	1.9%	0.9%
PR	68%	49%
DOR, median (months) (95% CI)	8.3 (7.6, 11.3)	6.0 (5.6, 11.1)
CR, complete response; PR, partial response		

The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response.

IPASS

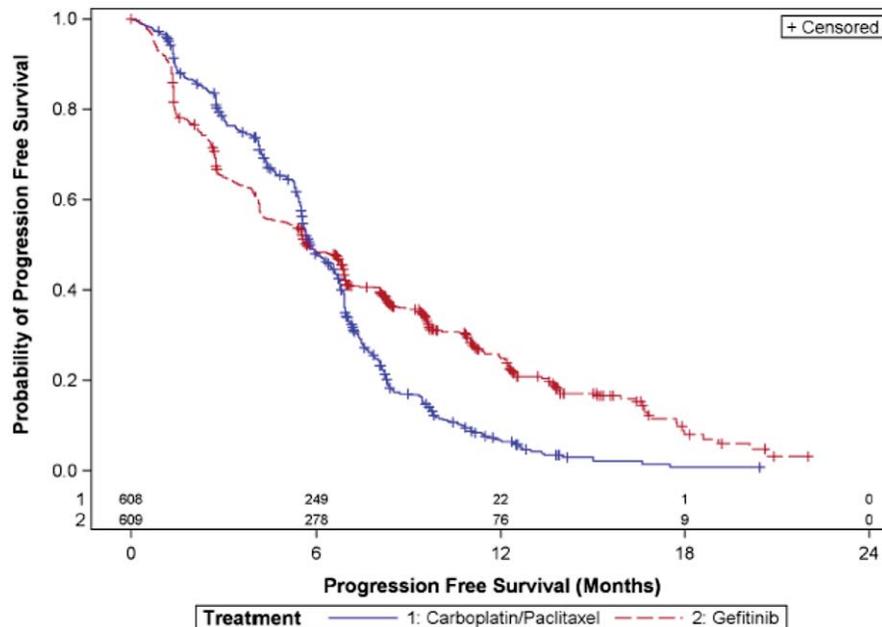
Efficacy from the single arm IFUM study was supported by the exploratory retrospective subgroup analysis of IPASS. IPASS was a randomized, multicenter, open-label trial conducted in patients with metastatic NSCLC receiving first-line treatment. The eligibility criteria of never or light ex-smokers, adenocarcinoma histology, and Asian ethnicity were designed to enrich for a study population likely to harbor an EGFR tumor mutation. Patients were randomized (1:1) to receive gefitinib 250 mg orally once daily (n=609) or up to six cycles of carboplatin/paclitaxel (n=608). Randomization was stratified based on PS, smoking history, gender, and enrollment center. The major efficacy outcome was progression-free survival (PFS) as assessed by the investigator. The primary objective was to demonstrate non-inferiority of gefitinib compared with chemotherapy (non-inferiority margin for PFS was a hazard ratio of 1.2).

From the 1217 patients enrolled, a total of 437 patients with evaluable tumor samples were retrospectively assessed for EGFR mutational status, of which 261 patients were determined to be EGFR positive by the same clinical trial assay as the IFUM study. Of these 261 patients, 186 (71%) had radiographic scans available for a retrospective assessment of BICR.

The demography and baseline characteristics of these 186 patients were median age of 59 years, age 75 years or older (7%), Asian (100%), female (83%), never smokers (96%), adenocarcinoma histology (100%), PS 0-1 (94%), similar baseline characteristics to the overall 1217 patients enrolled in IPASS.

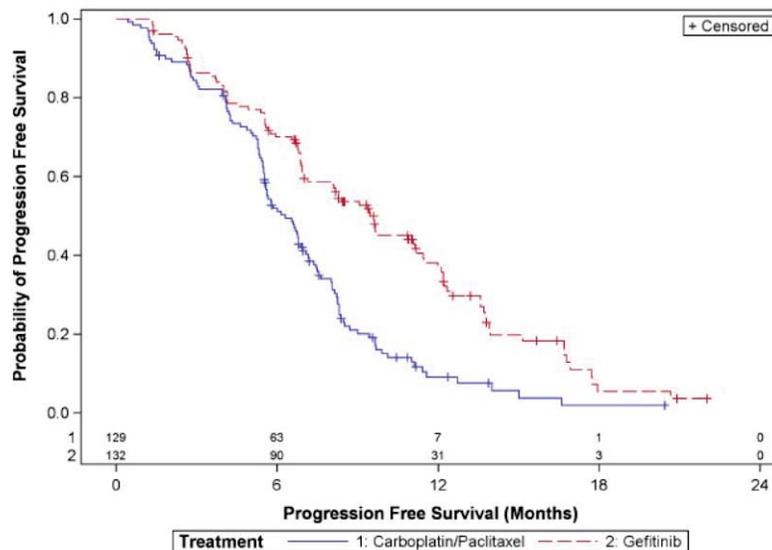
In the ITT population of 1217 patients enrolled, the median PFS for patients randomized to gefitinib was 5.7 months, and 5.8 months for those randomized to carboplatin/ paclitaxel, (HR=0.75; 95% CI 0.65, 0.85). This HR is not proportional as the Kaplan-Meier curves crossed near the median, indicating that there were two subgroups performing differently in the ITT population. Gefitinib has a negative effect relative to platinum doublet chemotherapy among patients with EGFR mutation “negative” tumor. Overall survival was no different in the ITT population. There were 223 deaths in the gefitinib arm and 227 deaths in the carboplatin/ paclitaxel arm. The median survival was 18.6 months in the gefitinib arm and 17.3 months in the carboplatin/ paclitaxel arm (HR=0.91; 95% CI 0.76, 1.10).

IPASS investigator PFS results in ITT population



In the exploratory subgroup of 261 patients deemed to be EGFR positive by retrospective testing, their appeared to be a PFS benefit in patients randomized to gefitinib (n=132) relative to patients randomized to carboplatin / paclitaxel (n=129). The median PFS was 9.5 months in the gefitinib arm and 6.3 months in the carboplatin/paclitaxel arm (HR=0.48; 95% CI 0.36, 0.64). Similarly, in the 186 patients with EGFR mutations who had central radiologic review of scans, their appeared to be a PFS benefit in patients randomized to gefitinib (n=88) relative to patients randomized to carboplatin / paclitaxel (n=98). In this analysis, the median PFS was 11 months in the gefitinib arm and 7.5 months in the carboplatin/paclitaxel arm (HR=0.55; 95% CI 0.38, 0.79).

IPASS retrospective investigator PFS subgroup analysis in EGFR mutation positive patients



Literature review of Japanese studies WJTOG3405 and NEJ002

Study WJTOG3405 (Mitsudomi *et al.* Lancet Oncology 2010) was a randomized study comparing gefitinib 250 mg daily with cisplatin/ docetaxel (80 mg/m² and 60 mg/m² in 21 day cycles) in patients with EGFR mutation-positive NSCLC conducted in Japan by the West Japan Oncology Group. Patients were required to have tumors positive for either Exon 19 deletion or exon 21 L858R substitution mutation. The primary endpoint was investigator PFS.

In WJTOG3405, the PFS favored patients allocated to gefitinib (n=86) over those assigned to cisplatin/ docetaxel (n=86). Median PFS was 9.6 months on the gefitinib arm and 6.6 months on the cisplatin/ docetaxel arm (HR=0.52; 95% CI 0.38, 0.72). The ORR was 62% for patients on the gefitinib arm and 32% for patients on the cisplatin/ docetaxel arm. The median OS was 35.5 months on the gefitinib arm and 38.8 months on the cisplatin/ docetaxel arm, however this is not interpretable due to cross-over and lack of statistical power.

Study NEJ002 (Maemondo *et al.* NEJM 2010) was a randomized study comparing gefitinib 250 mg daily with carboplatin/ paclitaxel (AUC 6 and 200 mg/m² in 21-day cycles) in patients with EGFR mutation-positive NSCLC conducted in Japan by the North East Japan Gefitinib Study Group. Patients with sensitive EGFR mutation were included but those with T790M resistance mutation were excluded. The primary endpoint was investigator PFS.

In NEJ002, the PFS favored patients allocated to gefitinib [n=114 (with 98 assessable for PFS)] over those assigned to carboplatin/ paclitaxel [n=114 (with 100 assessable for PFS)]. Median PFS was 10.8 months on the gefitinib arm and 5.4 months on the carboplatin/ paclitaxel arm (HR=0.32; 95% CI 0.24, 0.44). The ORR was 74% for patients on the gefitinib arm and 31% for patients on the carboplatin/ paclitaxel arm. The median OS was 27.7 months on the gefitinib arm and 26.6 months on the carboplatin/ paclitaxel arm, however this is not interpretable due to cross-over and lack of statistical power.

Primary Reviewers Conclusions:

Based on the totality of the data, Dr Kazandjian and Dr Yuan have concluded that the efficacy of gefitinib in the submitted studies (pivotal and supportive) are persuasive in demonstrating the efficacy of gefitinib for the proposed population of patients with metastatic NSCLC whose tumors harbor activating sensitizing EGFR mutations. I concur with this assessment.

8. Safety

I concur with the clinical reviewer's (Dr. Dickran Kazandjian) conclusions regarding the safety of gefitinib.

Safety Summary

The safety profile of gefitinib was primarily evaluated in a pooled analysis of 2,462 patients with advanced NSCLC who received gefitinib 250 mg daily in three randomized studies: IPASS (see efficacy section for a description), ISEL, and INTEREST.

ISEL was a randomized, multicenter, double-blind, placebo controlled trial of 1692 patients receiving second- or third- line treatment for metastatic NSCLC; 1129 patients received gefitinib 250 mg daily and 563 patients received placebo. The median duration of treatment with gefitinib was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), white (75%), Asian (21%), adenocarcinoma (48%), never smoker (22%), PS 0 or 1 (65%), PS 2 (29%), PS 3 (5%) and two or more prior therapies (31%).

INTEREST was a randomized, multicenter, open-label trial of 1466 patients receiving second-line treatment for metastatic NSCLC; 733 patients received gefitinib 250 mg daily and 733 patients received docetaxel. The median duration of treatment with gefitinib was 2.4 months. The study population characteristics were: median age 61 years, age less than 65 years (61%), female (36%), white (79%), Asian (21%), adenocarcinoma (54%), never smoker (20%), PS 0 or 1 (88%) and two or more prior therapies (16%).

The pooled safety database from the three randomized trials was used to evaluate for serious and uncommon adverse drug reactions.

The following serious or life threatening adverse reactions were observed in the pooled analysis across 2462 patients in clinical trials:

- Interstitial Lung Disease: occurred in 1.3% of patients; of these 0.7% were Grade 3 or higher and 0.1% were fatal
- Hepatotoxicity: ALT increases occurred in 11.4% of patients (all Grades) and 5.2% had Grade 3 or higher ALT. Bilirubin increases occurred in 2.7% of patients (all Grades) and 0.7% had Grade 3 or higher bilirubin. The incidence of fatal hepatotoxicity was 0.04%.
- Gastrointestinal perforation occurred in 0.1% of patients
- Severe or persistent diarrhea: grade 3 or 4 diarrhea occurred in 3% of patients
- Ocular disorders and keratitis: grade 3 ocular disorders occurred in 0.1% of patients
- Bullous and exfoliative skin disorders: erythema multiforme and dermatitis bullous were reported in 0.08% of patients.

Common adverse reactions were evaluated in ISEL. The most frequent adverse reactions in ISEL (incidence of >20% and greater than placebo) reported in gefitinib-treated patients were skin reactions (47%) and diarrhea (29%). The most frequent fatal adverse reactions in gefitinib-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

Approximately 5% of gefitinib-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event, of which 2.8% of gefitinib-treated patients discontinued due to an adverse drug reaction. The most frequent adverse reactions that led to discontinuation in patients treated with gefitinib were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

Selected Adverse Events Occurring at a rate of $\geq 5\%$ and an Increase of $\geq 2\%$ of gefitinib-treated Patients in ISEL

Adverse Reaction	Percentage (%) of patients			
	Gefitinib (N=1126)		Placebo (N=562)	
	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Skin and subcutaneous tissue disorders				
Skin reactions ¹	47%	2%	17%	0.4%
Nail disorders ²	5%	0.1%	0.7%	0%
Gastrointestinal disorders				
Diarrhea ³	29%	3%	10%	1%
Vomiting	14%	1.2%	10%	0.4%
Stomatitis ⁴	7%	0.3%	4%	0.2%
Metabolism and nutrition disorders				
Decreased appetite	17%	2.3%	14%	2.0%
General disorders and administration site conditions				
Pyrexia ⁵	7%	0.6%	6%	0.4%
Eye disorders				
Conjunctivitis/blepharitis/dry eye ⁶	6%	0%	3.2%	0%

¹ Includes Acne, Acne pustular, Dermatitis, Dermatitis acneiform, Dermatitis exfoliative, Drug eruption, Dry skin, Erythema, Exfoliative rash, Folliculitis, Pruritus, Pruritus generalised, Rash, Rash erythematous, Rash generalised, Rash macular, Rash macula-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin irritation, Skin toxicity, Xeroderma.

² Includes Ingrowing nail, Nail bed infection, Nail bed inflammation, Nail bed tenderness, Nail disorder, Nail dystrophy, Nail infection, Onychalgia, Onychoclasia, Onycholysis, Onychomadesis, Paronychia.

³ Includes Diarrhea, Feces soft, Frequent bowel movements.

⁴ Includes Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Lip ulceration, Mouth ulceration, Mucosal inflammation, Oral mucosal blistering, Oral mucosal eruption, Stomatitis, Tongue disorder, Tongue ulceration.

⁵ Includes Pyrexia, Chills.

⁶ Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Dry eye, Eye inflammation, Eye irritation, Eye pruritus, Eye swelling, Eyelid irradiation, Eyelid edema, Eyelids pruritus, Ocular hyperaemia.

Treatment Emergent Laboratory Abnormalities Occurring More Frequently in gefitinib-Treated Patients in ISEL

Adverse Reaction	Gefitinib		Placebo	
	All Grades %	Grade 3 and 4 %	All Grades %	Grade 3 and 4 %
ALT increased	38%	2.4%	23%	1.4%
AST increased	40%	2.0%	25%	1.3%
Proteinuria	35%	4.7%	31%	3.3%

Overall Safety Assessment: I concur with Dr Kazandjian that the overall safety assessment is consistent with that observed with other EGFR TKIs such as erlotinib and afatinib. Given that gefitinib is not dosed near the maximum tolerated dose of 500 mg daily and is a reversible inhibitor, the safety profile of the 250 mg daily dose may be more favorable than the other EGFR TKIs currently marketed, although the Applicant did not directly compare gefitinib with other EGFR TKIs. In addition, gefitinib clearly has a different safety profile than traditional cytotoxic chemotherapy (without myelosuppression or alopecia).

9. Advisory Committee Meeting

The NDA for gefitinib was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

Gefitinib is exempt from the pediatric study requirements of the Pediatric Research Equity Act in accordance with the provisions of 21 CFR 314.55. Gefitinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of patients with NSCLC that is EGFR mutation positive in August 2014.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues
- **Exclusivity or Patent Issues of Concern:** No issues. The Applicant notes that patent certification is not required for this 505(b)(1) application. The Applicant has requested 5-year exclusivity. Refer to exclusivity review.

- **Financial Disclosures:** No issues. The applicant enclosed form FDA 3454 regarding the financial interests and arrangements for clinical investigators who contributed to the covered clinical studies submitted in this application. Disclosure (form FDA 3455) was provided for investigators with disclosable financial interests, along with explanations for why these interests did not introduce bias into the clinical trials. I agree with Dr. Kazandjian's assessment that financial interests likely did not affect results of the key studies submitted to the NDA.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** Based on the review of preliminary inspectional findings, the data from IFUM generated by CRO (b) (4) who performed the function of the Blinded Independent Central Review (BICR) Vendor, submitted to the Agency in support of NDA 206995, appear reliable. The preliminary classification for the CRO (b) (4) is NAI.
- **Other Discipline Consults:** None
- **Other Outstanding Regulatory Issues:** None

12. Labeling

- **Proprietary name:** In December 2014, OSE/DMEPA concluded that the proposed proprietary name, Iressa, is acceptable.
- **OSE/ Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.
- **Patient Labeling Team:** The patient labeling team participated in labeling discussions.
- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.
- **Clinical labeling summary:** labeling negotiations are ongoing at the time of finalization of this memo. One outstanding issue is how the uncommon mutations of intermediate sensitivity (such as L861Q and G719X) will be described in labeling (sections (b) (4) and 14). Other changes include
 - Warnings and Precautions: added Bullous and Exfoliative Skin Disorders
 - Adverse Reactions: added post-marketing experience
 - Section 14: added more details on the eligibility of intermediate sensitizing mutations in IFUM (L861Q and G719X) and the limited response data, as well

as fact that T790M and insertion 20 and S7681 mutation positive patients were excluded. Removed [REDACTED] (b) (4)

[REDACTED] Included more qualitative description of IPASS retrospective subgroup analysis.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Traditional Approval

- Risk Benefit Assessment

Patients with metastatic NSCLC whose tumors harbor EGFR exon 19 deletion or exon 21 L858R substitution mutation have a serious and life-threatening disease, with unmet medical need and median survival ranging from 2 to 3 years. The single arm IFUM trial demonstrated that treating patients with EGFR sensitizing and activating mutations with gefitinib leads to a large magnitude of durable ORR, with ORR ranging from 50 to 70% (depending on BIRC or investigator assessment) with median DOR ranging from 6 to 8 months. The findings from the single arm IFUM study are supported by the retrospective analysis of IPASS, in which patients with EGFR mutations allocated to gefitinib had substantially longer PFS compared to those randomized to platinum doublet, as well as the two Japanese studies, in which patients prospectively identified to have EGFR activating sensitizing mutations randomized to gefitinib had longer PFS and improved ORR compared to patients randomized to platinum doublet chemotherapy.

The risks of gefitinib were acceptable compared to the benefits. Common adverse reactions (all Grades) over placebo rate include diarrhea (29% versus 10%) and skin reactions (47% versus 17%). Common laboratory abnormalities over placebo include liver enzyme elevations. Rare but serious adverse reactions include: ILD, gastrointestinal perforation, hepatotoxicity, severe ocular toxicity, bullous and exfoliative skin reactions, and severe diarrhea. In all, these toxicities appear to be similar to slightly less in magnitude than other EGFR TKIs in this class and provide an alternate and favorable risk profile compared to conventional chemotherapy.

Based on the favorable risk-benefit and demonstration of safety and efficacy, traditional approval is recommended.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The Applicant did not propose a REMS and the review teams did not identify the need for a REMS at this time to ensure the safe use of gefitinib.

- Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

GIDEON M BLUMENTHAL
06/04/2015