

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206995Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review

<b>Date</b>	July 13, 2015
<b>From</b>	Patricia Keegan
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	206995
<b>Applicant Name</b>	AstraZeneca Pharmaceuticals LP
<b>Date of Submission</b>	September 17, 2014
<b>PDUFA Goal Date</b>	July 17, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Iressa/ gefitinib
<b>Dosage Forms / Strength</b>	Tablets for oral administration/ 250-mg
<b>Approved Indication(s)</b>	<p>IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.</p> <p>Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.</p>
<b>Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	Dickran Kazandjian
Statistical Review	Weishi (Vivian) Yuan
Pharmacology Toxicology Review	G. Sachia Khasar
Drug Product/Substance Quality Review	Donghao (Robert) Lu
Biopharmaceutics Review	Salaheldin S. Hamed
Microbiology Quality Review	Robert J. Mello
Clinical Pharmacology Review	Robert N. Schuck
OPDP Consult	Marybeth Toscano
Patient Labeling Review	Barbara Fuller
OSI	Lauren Iacono-Connors
CDTL Review	Gideon Blumenthal
OSE/DMEPA	Davis Mathew
OSE/EPI	Davis Mathew
QT IRT Review	Dinko Rekcic

OND=Office of New Drugs  
 OPDP=Office of Prescription Drug Promotion  
 OSE= Office of Surveillance and Epidemiology  
 OSI=Office of Scientific Investigations  
 OSE=Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 CDTL=Cross-Discipline Team Leader

# Division Director Summary Review

## 1. Introduction

This New Drug Application for Iressa (gefitinib) seeks to re-introduce gefitinib into commercial marketing with the proposed indication for “the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.”

Specific issues discussed in this summary review were the use of genomic selection to identify the indicated patient population, use of supportive data from a second study in which the evaluation relied on a study endpoint other than the planned primary endpoint as well as reliance on subset analyses for determination of efficacy, and use of totality of the evidence across the major and supportive trial to draw conclusions regarding substantial evidence of effectiveness.

Gefitinib is a small molecule tyrosine kinase inhibitor that reversibly inhibits the kinase activity of epidermal growth factor receptor (EGFR). EGFR is expressed on the cell surface of both normal and cancer cells and plays a role in the processes of cell growth and proliferation. Certain EGFR mutations (predominantly exon 19 deletions or the exon 21 point mutation L858R) which occur in approximately 20% of adenocarcinoma histologic subtype of non-small cell lung cancer (NSCLC) have been identified as contributing to the promotion of tumor cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis. Through its inhibition of the kinase activity of EGFR, erlotinib prevents autophosphorylation of tyrosine residues associated with the receptor, leading to inhibition of downstream signaling and blocking EGFR-dependent cell proliferation. Although gefitinib has demonstrated inhibition of tyrosine kinase activity in cells with wild-type and those with EGFR “activating” mutations, the binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type EGFR, as discussed below, there was no evidence of activity of gefitinib in patients with EGFR wild-type adenocarcinoma of the lung in the subset of the IPASS study with poorer outcomes for patients receiving gefitinib as compared to chemotherapy.

Gefitinib was marketed from 2003 to 2012, when it was withdrawn from the market based on an inability to verify clinical benefit in multiple randomized trials that did not limit eligibility based on the mechanism of action; i.e., eligibility was not limited to patients with NSCLC bearing a known EGFR “activating” mutation. A description of the data supporting initial approval and the studies which failed to demonstrate clinical benefit are further described in Section 2 of this summary review.

The current application contains the results of a prospective, genetically-selected, clinical trial, the Iressa Follow-up Measure Study (IFUM), conducted in 106 patients receiving initial treatment for EGFR mutation-positive NSCLC, which demonstrated a clinically important overall response rate of 50% (95% confidence intervals: 41, 59) with a median duration of response of 6.0 months (95% CI: 5.6, 11.1 months) in patients receiving gefitinib 250 mg orally, once daily. This data is supported by a subgroup analysis of the IPASS trial, a randomized, active-controlled trial intended to demonstrate that treatment with gefitinib 250 mg daily was non-inferior with respect to overall survival to a standard platinum doublet (carboplatin and paclitaxel). FDA agreed that, based upon the mechanism of action of gefitinib, it was appropriate to conduct and provide the results of pre-specified exploratory subgroup analyses of the IPASS trial based on EGFR tumor mutation status in support of the proposed application. FDA relied on the results in this subset of 186 (15%) of the 1217 patients enrolled in the IPASS trial in whom EGFR mutation-positive adenocarcinoma of the lung was identified using an analytically validated test. The results in this subset yielded similar overall response rate as confirmed by independent review to those in the IFUM trial with an ORR of 67% (95% CI: 56, 77) and median duration of response of 9.6 months. In addition, the analysis of progression-free survival based on the independent review of images for both arms in the IPASS trial also favored the gefitinib arm [HR of 0.54 (95% CI: 0.38, 0.79)] with a median PFS of 10.9 months for patients randomized to gefitinib and 7.4 months for the patients randomized to receive carboplatin/paclitaxel chemotherapy in this subgroup. In contrast, PFS was inferior in the subgroup of patients with NSCLC whose tumors had no detectable EGFR mutation (HR: 2.85; 95% CI: 2.05, 3.98) randomized to gefitinib as compared to carboplatin/paclitaxel. In this subgroup, the median PFS was only 1.5 months in the gefitinib arm and 5.5 months in the carboplatin/paclitaxel arm; thus it is appropriate to restrict the indication to patients with EGFR mutation-positive NSCLC.

The adverse drug reaction profile was similar to that observed during the initial approval. In a safety database of 2462 patients with NSCLC receiving gefitinib 250 mg orally once daily, the most serious adverse reactions were interstitial lung disease, hepatotoxicity, gastrointestinal perforation, severe or persistent diarrhea, and ocular disorders including keratitis. The incidence of severe or life-threatening adverse drug reactions was hepatotoxicity (manifesting as liver test abnormalities) and diarrhea, at 1.4% and 3% respectively. The incidence of fatal adverse reactions for each of these was less than 1%.

The most frequent adverse reactions (incidence of >20% and greater than placebo) reported in 1126 gefitinib-treated patients were skin reactions (47%) and diarrhea (29%) enrolled in the ISEL trial, a randomized, placebo-controlled trial conducted in patients with NSCLC who were unable to tolerate or had experience disease progression on or within 90 days of receiving first- or second-line chemotherapy. Approximately 5% of gefitinib-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%). The most frequent fatal adverse reactions in gefitinib-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

## 2. Background

### *Indicated Population and Available Therapy*

Based on the NCI SEER database, there will be an estimated new 221,200 new cases of lung cancer and an estimated 158,040 deaths due to lung cancer in the US in 2015. Approximately 85% of lung cancers are non-small cell lung cancer, with the most common subtype of NSCLC being adenocarcinoma. The incidence of EGFR mutations in patients with adenocarcinoma is approximately 20%. There are two FDA-approved drugs for the treatment of EGFR-mutation positive adenocarcinoma; based on these recent approvals, the “natural history” of this genetically distinct form of lung cancer is evolving but at present is not clearly defined.

### *Available therapy*

On May 14, 2013, **erlotinib** was approved for the “first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Safety and efficacy of TARCEVA have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.”

Approval was based primarily on the results of single, investigator-initiated, randomized (1:1), open-label, active-controlled trial (EURTAC trial) conducted in 174 patients receiving first-line treatment for metastatic NSCLC whose tumors had EGFR exon 19 deletion or exon 21 substitution (L858R) mutation as detected by a clinical trial assay at a central academic study site. The trial demonstrated a statistically significant improvement in investigator-determined PFS for patients randomized to erlotinib compared to those randomized chemotherapy [Hazard ratio (HR) 0.34 (95% confidence intervals (CI): 0.23, 0.49),  $p < 0.001$ ] with median progression-free survivals of 10.4 months in the erlotinib arm and 5.2 months in the chemotherapy arm. The overall response rate was substantially higher (65% vs. 19%) for the erlotinib arm compared to the chemotherapy arm. A protocol-specified analysis of overall survival conducted at the time of the final analysis of PFS, after 109 deaths (63% of the study population), showed no statistically significant difference in survival between the TARCEVA and chemotherapy arms [HR 0.93 (95% CI: 0.64, 1.35)] with median survival times of 22.9 months in the erlotinib arm and 19.5 months in the chemotherapy arm.

On July 12, 2013, **afatinib** was approved for the “first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations.”

This approval was primarily based on a single randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung. The trial demonstrated a statistically significant improvement in PFS as determined by the IRC for patients randomized to afatinib [HR 0.58 (0.43, 0.78),  $p <$

0.001], with median PFS of 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. In addition, the afatinib also had substantially higher overall response rates (50% vs. 19%). There was no statistically significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis [HR 0.91 (0.66, 1.25), p=0.55], with a median survival of 28 months in each arm.

#### *Pre-Submission History*

May 5, 2003: NDA 21399 for Iressa (gefitinib) was approved under the provisions of 21 CFR 314.510 (Subpart H) with the following indication “as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The effectiveness of IRESSA is based on objective response rates. 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 in first-line treatment of non-small cell lung cancer showed no benefit from adding IRESSA to doublet, platinum-based chemotherapy. Therefore, IRESSA is not indicated for use in this setting.”

Approval was granted based on demonstration of durable objective response rates in patients receiving third-line treatment for advanced NSCLC. The major efficacy trial supporting approval was a single, multicenter, two-arm clinical trial conducted in 216 patients who were randomized to receive gefitinib 250 mg daily or gefitinib 500 mg daily. The data supporting approval were obtained in a subset of these patients with unmet medical need, i.e., 142 patients whose disease had progressed after at least two prior chemotherapy regimens including a platinum drug and docetaxel. The overall response rate (ORR) for the 250 and 500 mg arms combined was 10.6% (95% CI: 6%, 16.8%) and was unusually prolonged for this heavily pre-treated population, with a median duration of response of 7 months (range 4.4-18.6+ months). As noted at the time, the response rates were higher in females (17.5% vs. 5.1%) as compared to males, non-smokers (29.4% vs. 4.6%) as compared to former or current smokers and those with pure adenocarcinoma (12.4% vs. 6.7%) as compared to those with other NSCLC histologic subtypes (squamous cell carcinoma, large cell, undifferentiated, adenosquamous, and not specified). These findings were supported by evidence of durable objective responses in patients receiving second-line therapy (in patients whose disease had progressed following platinum-based doublet therapy).

During review of this NDA, the results of two large, multicenter, randomized trials comparing the safety and efficacy of cisplatin-based doublet chemotherapy plus gefitinib to chemotherapy became available. Both of these trials showed no evidence of clinical benefit (improved survival, progression-free survival or response rate); therefore the NDA was referred to the Oncologic Drugs Advisory Committee (ODAC). A majority of the ODAC members advised that despite the lack of clinical benefit in two large studies of gefitinib in combination with standard first-line NSCLC chemotherapy, the durable response rate observed in patients with resistant or refractory NSCLC reasonably likely to predict the clinical benefit of gefitinib in the third-line treatment of NSCLC. As noted by the medical reviewer, the Committee indicated that, for NSCLC in the third line setting where there are no viable treatment options, a 10% response rate is meaningful, and shows evidence of biologic activity of the drug. The reason for failure of the first line trials remains unexplained, and requires further study.”

The following post-marketing commitments, which were required to verify and describe clinical benefit, were identified in the approval letter:

- To conduct, submit, and publish the final study report for Protocol 1839IU0709 entitled "A randomized phase III survival study comparing ZD1839 (Iressa™) plus best supportive care (BSC) versus placebo plus BSC in subjects with advanced NSCLC who have received one or two prior regimens and are refractory or intolerant to their most recent regimen." Survival is the primary study endpoint. We refer you to our letter of April 1, 2003 detailing the Division response to your Special Protocol Assessment request. Further, as stated in your letter of February 19, 2003 the first patient should be enrolled in this study in early July 2003. Enrollment should be completed by April 2005, and study results should be submitted to the Division in October 2005.
- To conduct, submit, and publish the final study report for a randomized trial comparing gefitinib and taxotere in NSCLC. The primary endpoints should be survival and time to progression. A secondary endpoint should evaluate cancer-related symptoms. The study should enroll at least 800 patients. A detailed protocol should be submitted to the Division as an SPA by June 13, 2003, with the first patient enrollment by November 2003 and the study report submitted to the Division by December 2006.
- To conduct, submit, and publish the final study report for a randomized, controlled, double blind, study comparing ZD1839 treatment with best supportive care in refractory, symptomatic, stage III/IV NSCLC patients (PS 0-2, LCS  $\leq$ 20). Symptom improvement should be the primary endpoint of this study. A detailed protocol should be submitted to the Division as an SPA by June 13, 2003, with the first patient enrollment by November 2003 and the study report submitted to the Division by June 2005.

On June 17, 2005, based on the failure to verify clinical benefit in three additional adequate and well-controlled clinical trials, FDA requested and AstraZeneca agreed to restrict product labeling. This was based on primarily on the results of Study ISEL (D7913C00709) a double-blind, placebo-controlled trial randomized 1692 patients with treatment-resistant NSCLC or inability to tolerate chemotherapy to receive either gefitinib 250 mg daily plus Best Supportive Care or placebo plus Best Supportive Care. Patients were required to have received 1 or 2 prior chemotherapy regimens with disease progression while receiving or within 90 days of the last dose of chemotherapy or to be unable to tolerate the most recent prior chemotherapy regimen. The study failed to demonstrate an improvement in overall survival, the primary endpoint, with a hazard ration of 0.89,  $p=0.11$ , and median survival of 5.6 vs 5.1 months for the gefitinib and placebo arms, respectively. In addition, data from two other trials were considered: Study IBRESE, a double-blind, placebo-controlled, multicenter, randomized study the effects on pulmonary disease-related symptoms with gefitinib and best supportive care (BSC) to placebo plus BSC in symptomatic patients with advanced NSCLC who had received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen, which was terminated prematurely, and Study INTEREST (D791GC0001), a randomized, open-label, international, multicenter, study designed to demonstration non-inferiority in survival for gefitinib to intravenous docetaxel in patients with locally advanced or metastatic recurrent NSCLC who have previously received platinum-based

chemotherapy, which although incomplete, was considered likely to be uninterpretable in light of the results of ISEL trial. Finally, FDA considered the results randomized trials evaluating the efficacy of gefitinib as adjuvant treatment and as maintenance therapy following first-line chemotherapy also failed to verify the clinical benefit of gefitinib. As a result of these data, the accelerated approval was further revised to include a limited distribution program and the indication was revised as follows

“IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.”

As stated in the approval letter for this supplement, AstraZeneca “will limit distribution of this drug under a risk management plan called the Iressa Access Program, to the following patient populations:

- patients currently receiving and benefiting from Iressa;
- patients who have previously received and benefited from Iressa; and
- previously enrolled patients or new patients in non-IND clinical trials approved by an IRB prior to June 17, 2005.

December 2009: A meeting was held to discuss the ability to use the clinical efficacy results from the IPASS study to support an efficacy supplement to NDA 21399. 2009 meeting with AZ. FDA noted that the PFS analysis reported for the ITT population for this open-label study was not confirmed by independent review and that there was no evidence available for effects on OS, particularly in light of multiple prior negative trials and given that the IPASS trial was conducted entirely outside the US. During the meeting, FDA agreed that a subgroup analysis of PFS as determined by an independent review committee in patients with EGFR mutation-positive NSCLC as determined by an analytically validated test could be considered for review. In addition, AZ would need to provide justification for extrapolation of the data to the US population.

February 1, 2011: AstraZeneca submitted requesting withdrawal of approval of NDA 21399, effective September 30, 2011, and waiving any opportunity for a hearing. FDA acknowledged this request on February 4, 2011.

April 25, 2012 – The Federal Register published notification of the voluntary withdrawal of marketing approval of Iressa.

March 11, 2014: A meeting was held under pIND 120992 to discuss a proposal to submit a New Drug Application (NDA) for Iressa for the first-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test. AZ proposed that the

efficacy data to be submitted in support of this NDA would consist primarily of data from (1) the subset of patients enrolled in the Study IPASS who were determined to be EGFR-mutation-positive on a retrospective analysis, constituting approximately 20% of the 1217 patients registered and randomized in this clinical trial and (2) efficacy data for all patients enrolled in Study IFUM, a single arm study conducted in patients with prospectively-identified EGFR mutation-positive NSCLC. FDA stated that they considered the efficacy results and independent confirmation of objective response rate (ORR) and duration in the IFUM study as the primary data to be reviewed in support of the benefit-risk assessment in the NDA submission. FDA further stated that the retrospective analysis in the convenience subset of IPASS would be considered supportive of the IFUM study results. FDA would also consider supportive data from the ITT population enrolled in IPASS and the published results from two randomized trials conducted prospectively in Japanese patients with EGFR mutation-positive NSCLC (NEJ002 and WJTOG3405) for which AZ did not intend to provide datasets.

August 26, 2014: FDA granted orphan drug designation for gefitinib for the indication of treatment of epidermal growth factor receptor (EGFR) mutation-positive, non-small cell lung cancer.

### **3. Chemistry, Manufacturing, and Controls (CMC)/ Biopharmaceutics/Microbiology**

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 48 months at controlled room temperature. There are no outstanding issues that preclude approval.

AstraZeneca submitted an amendment to pre-IND 120992 describing the differences in CMC and facilities between NDA 21399 and this NDA 206995. The quality review focused on the differences in chemistry, manufacturing and controls between the two NDAs using risk based approaches to assess the product development, manufacturing process and quality control. As noted by the quality reviewer, the clinical studies supporting approval of this NDA were conducted with clinical batches that are identical qualitatively and quantitatively to the proposed commercial batches. The NDA also contained dissolution data and references a comparative in-vivo bioavailability study from NDA 21-399 to support the selection of the dissolution method and acceptance criterion. The proposal to waive all microbial enumeration testing (release and stability) was granted by the quality microbiology reviewer since AstraZeneca has demonstrated adequate control over the manufacturing processes and has batch data supporting this control. Finally, the quality reviewers confirm during labeling negotiations under this NDA that dissolution of Iressa in water prior to oral administration, which had been previously reviewed under NDA 21399, did not alter its bioavailability.

No post-marketing commitments were requested.

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

All nonclinical toxicology studies required to support the approval of gefitinib were reviewed under NDA 21399. Literature reports of nonclinical pharmacology studies were submitted under NDA 206955 to support the mechanism of action for the indicated population. These studies support the proposed indication, which is restricted to patients with EGFR mutation-positive NSCLC. In these studies, gefitinib inhibited EGFR-induced autophosphorylation of mutant receptors (IC<sub>50</sub>=15 nM) at lower concentrations than wild-type receptors (IC<sub>50</sub> 15nM vs. 100 nM) for cell lines containing EGFR mutation-positive (L858R) than for those with wild type EGFR, respectively. Inhibition of L858R EGFR phosphorylation resulted in inhibited of the phosphorylation of ERK 1-2 and AKT, which are downstream in the EGFR pathway. In nude mouse tumor xenografts, inhibition of tumor growth was observed both in xenografts with the L858R or exon 19 deletions of EGFR and in tumor xenografts with wild type EGFR; however tumor regression was observed only in tumor xenografts with EGFR L858R or exon 19 deletions (not in wild type EGFR xenografts).

The nonclinical pharmacology/toxicology reviewer concurred with the final labeling describing Use in Specific Populations (8.1-8.3), with regard to description of risks based on nonclinical studies conforming to the format of the Pregnancy and Lactation Labeling Rule and to support the duration of contraceptive use.

## 5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology/pharmacogenomics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

There was no evidence of an exposure-response (E-R) relationship for efficacy (overall response rate) based on an E-R analysis of data from the IFUM trial; nor was a dose-response effect suggested by the ORR observed in clinical trials in which patients were randomized to receive gefitinib 250 mg daily or gefitinib 500 mg daily. However, there was an apparent correlation between exposure (AUC 5000 ng\*hr/mL) and the risk of interstitial lung disease (ILD) identified in an E-R analysis based on an observational study (study code: V-15-33) where sparse PK samples were collected in Japanese patients with advanced/recurrent NSCLC patients (n=186) with ILD supplemented by data randomly selected patients without ILD. In the IFUM, the risk of diarrhea appeared to increase with increasing exposure; however there was no apparent association between exposure and the risk of rash.

Based on the extensive metabolism of gefitinib by cytochrome P450 enzymes, drug interaction studies were performed. These demonstrated that a strong CYP3A4 inhibitor (itraconazole) increased the AUC of gefitinib by 80% and the C<sub>max</sub> by 51% and that a strong CYP3A4 inducer (rifampicin) decreased gefitinib AUC by 83% and C<sub>max</sub> by 65% when gefitinib was

administered at 250 mg daily. No dose adjustment is recommended when gefitinib is administered with a strong CYP3A4 inhibitor based on the tolerability of a 500 mg oral daily dose in clinical trials. However, labeling does recommend an increase in the gefitinib dose to 500 mg daily when gefitinib is administered with a strong CYP3A4 inducer in order to ensure that the gefitinib exposure remains within the therapeutic range.

Similarly, based on studies demonstrating that increased gastric pH (maintained at pH >5) reduced AUC by 47% and C<sub>max</sub> by 70%, product labeling recommends avoiding concomitant use of proton pump inhibitors, if possible, and modify scheduling of gefitinib when in patients taking H<sub>2</sub>-receptor antagonists or antacids concurrently.

Adequate data from clinical trials were provided to allow a conclusion that there was no large change (i.e., > 20 ms) in the QTcF interval.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

The scope of the program was adequate to demonstrate efficacy in a genetically-defined subpopulation of patients with NSCLC. The NDA contained the results of two clinical studies, the IFUM trial and the analysis of the subset of patients with confirmed, EGFR mutation-positive NSCLC enrolled in the IPASS study, which demonstrated durable objective response rates in both studies and evidence of a clinically meaningful and statistically robust improvement in progression-free survival over platinum-based doublet chemotherapy (standard of care) in the genetically-defined subset of patients in the IPASS trial. In addition, AstraZeneca also submitted summaries of Studies WJTOG3405, NEJ002, iTARGET, NEJ001, and NEJ003 as supportive evidence of the efficacy and safety of gefitinib in patients with EGFR mutation-positive NSCLC. While these literature reports indicate consistent findings (improved ORR and longer PFS in gefitinib-treated patients), these data were not relied upon for regulatory decision-making.

### *Reliability of the data*

Based on the results of FDA's bioresearch monitoring inspections of the [REDACTED] (b) (4), and six clinical investigational study sites, the data generated at these sites and submitted to the NDA were deemed reliable and the clinical trial was conducted in accordance with Good Clinical Practices and ethical principles.

### *IFUM (D791AC00014): Trial design and Results*

The major efficacy study supporting approval of this NDA was a multicenter, open-label, single-arm trial conducted in patients receiving first-line treatment for metastatic, EGFR mutation-positive NSCLC. Key eligibility criteria for this trial were evidence an EGFR "activating: mutation (deletion in EGFR exon 19 or a L858R, L861Q, or G719X substitution

mutation) but no evidence of a “resistance” mutation (T790M, S 768I mutation, or exon 20 insertion) using an analytically validated clinical trial assay.

In the original protocol, the primary objective was objective response rate (ORR) according to RECIST v1.1 as evaluated by study investigators; however for regulatory purposes the primary objective was ORR as determined by a (b) (4), who performed the blinded independent central review (BICR). A key secondary objective was determination of the duration of response (DOR). was an additional outcome measure. All patients received gefitinib 250 mg orally, once daily, until disease progression or unacceptable toxicity.

A total of 107 patients were enrolled and treated; one patient was excluded from efficacy analyses based on determination within 3 weeks of entry that the patient was ineligible (had an EGFR exon 20 insertion mutation). The study population characteristics were: median age 65 years, age 75 years or older (25%), age less than 65 years (49%), white (100%), female (71%), never smokers (64%), WHO PS 0 (45%), WHO PS 1 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%).

The vast majority (96%) of patients had either exon 19 deletions (65%) or L858R substitution (31%); two patients each had tumors harboring L861Q or G719X substitution mutation. Tumor samples from 87 patients were tested retrospectively using the *therascreen*<sup>®</sup> EGFR RGQ PCR Kit, which confirmed the EGFR mutation status.

Efficacy results from the IFUM trial are summarized below, abstracted from the package insert.

**Table 1 – Efficacy Results in Study 1**

Efficacy Parameter	BICR <sup>1</sup> Assessment (n=106) <sup>2</sup>	Investigator Assessment (n=106)
Objective Response Rate <sup>3</sup> (95% CI)	50% (41, 59)	70% (61, 78)
Complete Response Rate	0.9%	1.9%
Partial Response Rate	49%	68%
Median Duration of Response (months) (95% CI)	6.0 (5.6, 11.1)	8.3 (7.6, 11.3)

<sup>1</sup> BICR, Blinded Independent Central Review

<sup>2</sup> 17 patients without target lesion at baseline detected by BICR were deemed non responders

<sup>3</sup> Determined by RECIST v 1.1

The response rates were similar (b) (4) in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations (b) (4). Two

partial responses were observed in Both (b) (4) patients (b) (4) G719X substitution mutation (b) (4) with (b) (4) responses (2.8 (b) (4) months and 5.6 (b) (4) months). One of two patients (b) (4) L861Q substitution mutation achieved a partial response with (b) (4) response (2.8 (b) (4) months).

*IPASS (D791AC00007): trial design and results*

The IPAS trial was a randomized (1:1), multicenter, open-label trial conducted in Asia comparing the safety and efficacy of gefitinib to platinum-based doublet chemotherapy as initial treatment for Stage IIIB or Stage IV NSCLC. The trial was designed to establish that gefitinib treatment was non-inferior to carboplatin/paclitaxel doublet chemotherapy with regard to survival. The trial enrolled a “clinically enriched population” based on characteristics identified in the original approval of gefitinib correlating with a greater response: Asian ethnicity, light ex-smokers or non-smokers, and adenocarcinoma histologic subtype of NSCLC. Patients were randomized (1:1) to receive gefitinib 250 mg once daily until disease progression or unacceptable toxicity or up to 6 cycles of carboplatin/paclitaxel chemotherapy.

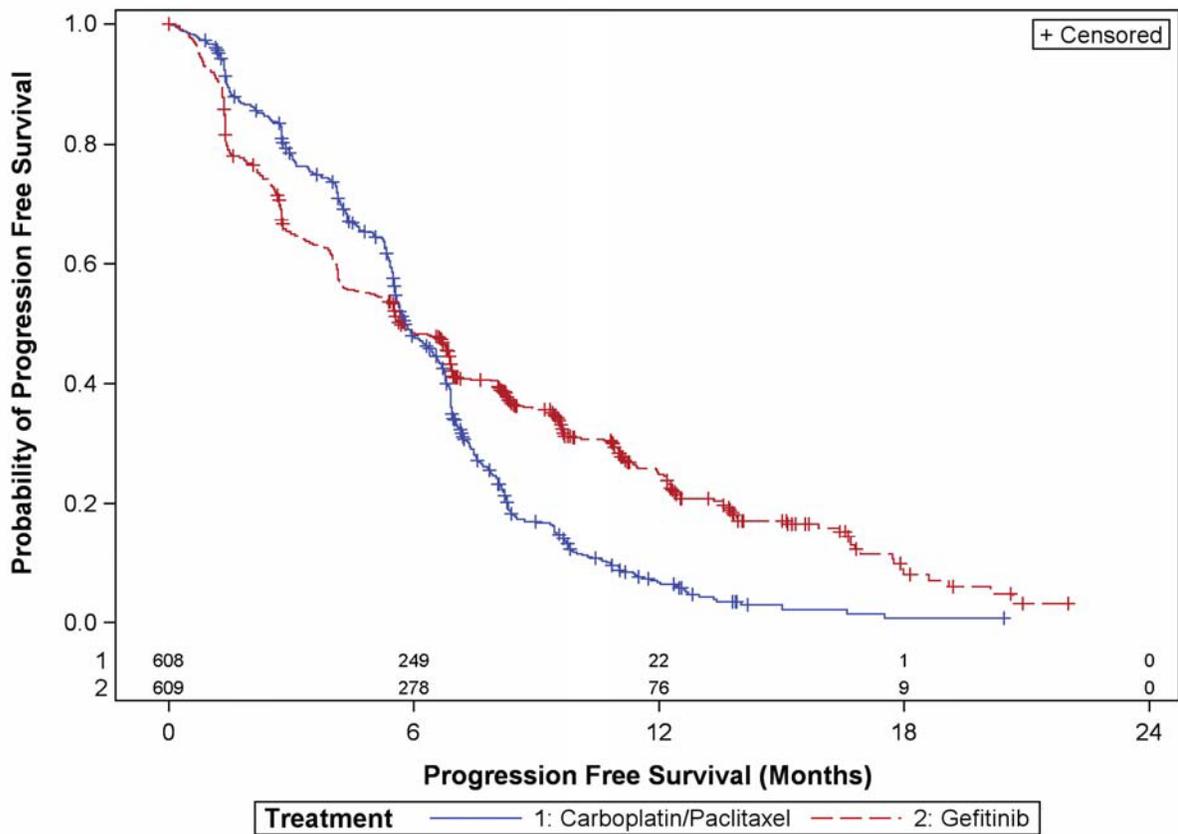
For regulatory purposes, the major efficacy objectives were determination of ORR and progression-free survival in the subset of patients with (1) EGFR mutation-positive NSCLC using the same analytically validated assay as in the IFUM trial and (2) baseline and follow-up data, including radiographic images, available for independent radiologic review by the BICR. This decision was based on the known mechanism of action of the drug and evidence, based on retrospective analysis, that clinical enrichment is an imperfect predictor of the presence of EGFR mutation-positive NSCLC.

A total of 1217 patients were enrolled; of these 36% of patients (n=437) had adequate tissue samples available for re-analysis with 40% having an EGFR mutation-positive tumor without a resistance mutation; 16% having an EGFR resistance mutation (T790M alone or in combination with other mutations or exon 20 insertion)-positive tumor, and 56% having no evidence of an EGFR mutation in tumor samples. There were 186 (15%) patients among the study population available for inclusion in the analysis subset, based on confirmation of EGFR mutation-positive NSCLC by central testing and availability of radiographic scans available for a retrospective assessment by BICR. Within this subset, 88 patients were randomized to receive gefitinib and 98 were randomized to receive carboplatin/paclitaxel-treated patients. Among these 186 patients, the median age was 59 years, all were Asian, 83% were female, 96% were never smokers, and all had adenocarcinoma histology and 94% had an ECOG performance status of 0 or 1.

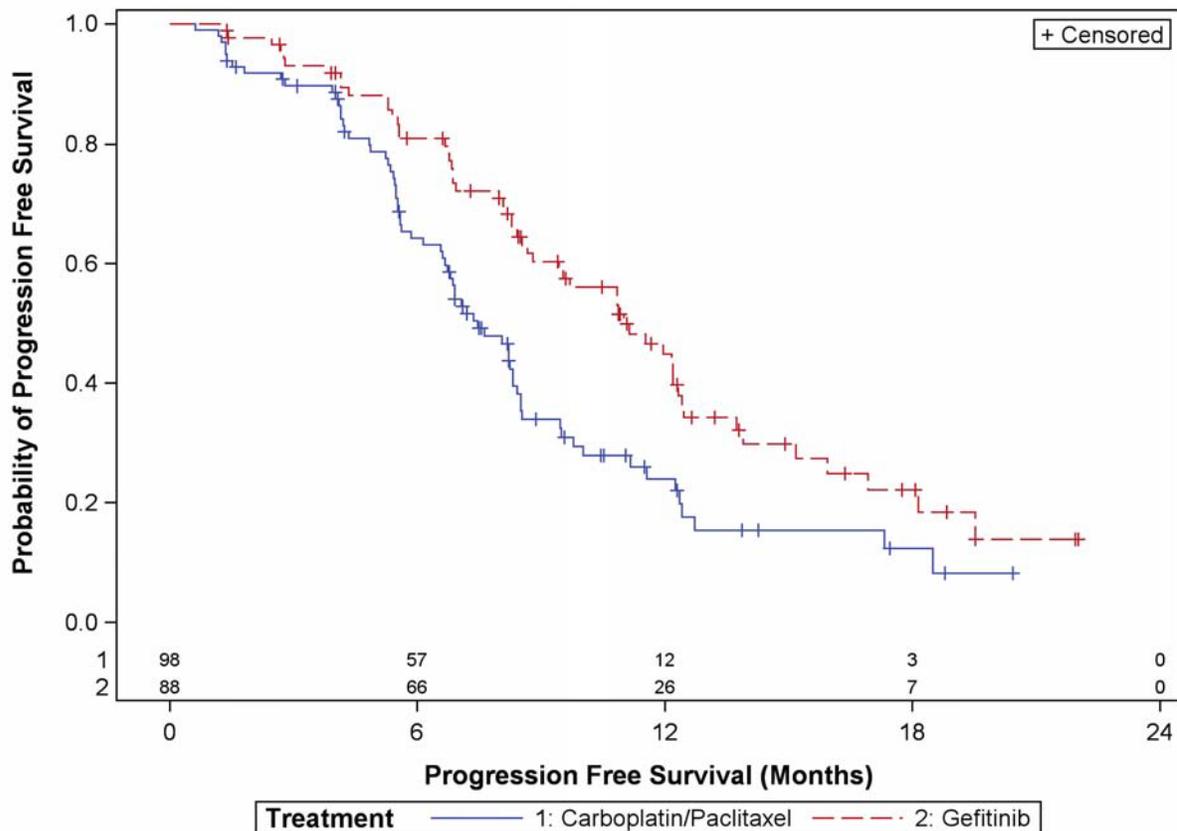
As determined by the BIRC, the overall response rate was 67% (95% CI: 56, 77) with a median duration of response of 9.6 months in the gefitinib arm compared with 41% (95% CI: 31, 51) with a median duration of response of 5.5 months for those randomized to carboplatin/paclitaxel. In addition, the hazard ratio for PFS as determined by the BIRC favored the gefitinib arm [HR of 0.54 (95% CI: 0.38, 0.79)] with a median PFS of 10.9 months for those randomized to gefitinib compared to 7.4 months for those randomized to carboplatin/paclitaxel-treated patients.

In exploratory subgroup analyses of patients with retrospectively determined, EGFR tumor mutation status in the IPASS trial, treatment with gefitinib resulted in worse outcomes among patients without an EGFR mutation. Based on investigator-assessed PFS in patients with EGFR mutation-positive NSCLC, there was a 52% reduction in the immediate risk of disease progression or death (HR: 0.48; 95% CI: 0.36, 0.64) for patients randomized to gefitinib as compared to those randomized to carboplatin/paclitaxel, with a 3.2 month improvement in median PFS (9.5 months and 6.3 months). In contrast, PFS was inferior in the subgroup of patients with NSCLC whose tumors had no detectable EGFR mutation (HR: 2.85; 95% CI: 2.05, 3.98) randomized to gefitinib as compared to carboplatin/paclitaxel. In the EGFR wild type subgroup, the median PFS was only 1.5 months in the gefitinib arm and 5.5 months in the carboplatin plus paclitaxel arm. The Kaplan-Meier curves for the intent-to-treat population based on investigator assessment and in the EGFR-mutation-positive subgroup, as determined by BICR, are abstracted from Dr. Yuan’s review and reproduced below

**K-M Curves for Progression Free Survival (Investigator-Determined) in the Overall Study Population**



### K-M curves for Progression-Free Survival (BIRC-determined) in the Subgroup of Patients with EGFR Mutation-Positive NSCLC



## 8. Safety

### *Size of the database*

Extensive safety data are available from the marketing experience with gefitinib and multiple clinical trials conducted and submitted to NDA 21399. Thus, there are no concerns regarding unidentified safety signals with this drug. For the purpose of characterizing safety in product labeling, data from three randomized clinical trials conducted in patients with NSCLC were used to generate information on the incidence of serious adverse reactions as described in the Warnings and Precautions section and data from a larger, randomized, placebo-controlled trial were used to identify common adverse reactions, as described in section 6 of product labeling. These three trials were:

- The IPASS trial, a randomized (1:1), active-controlled study conducted in 1217 Asian patients receiving first-line treatment of metastatic NSCLC; in which 607 received gefitinib and 589 patients received carboplatin/paclitaxel.
- A randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1692 patients receiving second- or third-line treatment for metastatic NSCLC, in which 1126 patients received gefitinib 250 mg daily and 562 patients received placebo.

- A randomized (1:1), multicenter, open-label trial conducted in 1466 patients receiving second-line treatment for metastatic NSCLC, in which 729 patients received gefitinib 250 mg daily and 715 patients received docetaxel.

*Major safety concerns related to labeling*

The following serious safety concerns were identified at the time of the original approval for gefitinib and are included in the Warnings and Precautions section of the agreed-upon labeling for the current NDA

- Interstitial lung disease (ILD) or ILD-like adverse drug reactions consisting of lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis occurred in 1.3% of gefitinib-treated patients (n=2462) in clinical trials of NSCLC; of these, 0.7% were Grade 3 or higher and 3 cases were fatal.
- Several liver test abnormalities indicated hepatotoxicity was observed in gefitinib-treated patients (n=2462) across clinical trials; the incidence of fatal hepatotoxicity was 0.04%. Across clinical trials, the incidences of Grade 3 or higher liver test abnormalities were 5.1% (ALT), 3.0% (AST), and 0.7% (bilirubin).

The following additional serious safety concerns have been identified since 2005 (the most recent approved labeling under NDA 21399) and are included in product labeling:

- Gastrointestinal perforation occurred in 0.1% of gefitinib-treated patients (n=2462) in clinical trials.
- Grade 3 or 4 diarrhea occurred in 3% of gefitinib-treated patients (n=2462) across clinical trials.
- The incidences of the following ocular disorders in gefitinib-treated patients (n=2462) across clinical trial were keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, and blepharitis and dry eye (6.7%). The incidence of Grade 3 ocular disorders was 0.1%.
- Serious and life-threatening bullous skin conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme were observed in gefitinib-treated patients. The incidence of erythema multiforme and dermatitis bullous was 0.08% in gefitinib-treated patients (n=2462) in clinical trials.

*Post-marketing data*

Given the availability of safety data from 2462 gefitinib-treated patients enrolled in controlled clinical trials data which provided better estimation of the incidence of serious adverse drug reactions, FDA relied primarily on clinical study data to describe the risks of gefitinib. Adverse drug reactions identified only in the post-marketing reports (cystitis, hemorrhagic cystitis, and cutaneous vasculitis) were described in the appropriate subsection of Adverse Reactions in product labeling.

*Final labeling recommendations (see section 12 of this summary review)*

*REMS, PMRs and PMCs:*

I concur with the review team that a REMS is not required to ensure safe and effective use of gefitinib in the indicated population.

## 9. Advisory Committee Meeting

Gefitinib is not a new molecular entity. Gefitinib was approved under NDA 021399 and subsequently voluntarily withdrawn from the market for reasons other than safety. It was not referred for review to the Oncologic Drugs Advisory Committee because Iressa is not the first drug in its class (tyrosine kinase inhibitor of EGFR pathway); the evaluation of the safety data did not raise significant safety or efficacy issues in the intended population; and the application did not raise significant public health questions on the role of Iressa in the treatment of a disease.

## 10. Pediatrics

This NDA is not subject to the requirements of the Pediatric Research Equity Act (PREA) because gefitinib received orphan drug designation for treatment of epidermal growth factor receptor (EGFR) mutation-positive, non-small cell lung cancer on August 26, 2014.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

- Proprietary name: On December 15, 2014, FDA issued a letter notifying AstraZeneca that the proposed proprietary name, Iressa, was acceptable.
- Physician labeling
  - Indications and Usage: Removed (b) (4)  
(b) (4) Limitation of use revised to indicate that safety and efficacy are not established in patients with EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitutions. While it is true that patients with EGFR wild type tumors have been shown not to benefit from gefitinib as first-line therapy, this population is clearly excluded from the indication.
  - Dosage and Administration: Edited for brevity and essential information.
  - Dosage Forms and Strength: editorial changes only
  - Contraindications: removed (b) (4)
  - Warnings and Precautions: Edited for brevity and removed (b) (4)  
(b) (4)  
Added specific information on the risks of GI perforation and removed (b) (4)  
(b) (4)  
Retitled subsection on Gastrointestinal (b) (4) to provide greater clarity on the specific risk (i.e., severe or persistent diarrhea). Provided specific risk information for

- ocular disorders and added new subsection on the risk of bullous disorders. Included risk of embryofetal toxicity in the Warnings section.
- Adverse Reactions: Provided description of clinical trials and demographic information for the clinical trials providing information on adverse drug reactions, consistent with FDA guidances on this section of product labeling. Revised tabular listing of adverse events to provide data based on appropriate SMQ's or composite terms to avoid underestimation of adverse drug reactions and limited data to those events occurring more frequently than in the placebo arm. Inserted table to display laboratory abnormalities and included clinical significant adverse reactions identified only in post-marketing reports. Drug Interactions: Modified subsections on drug interactions to provide specific recommendations for patients receiving strong CYP3A4 inducers and to describe data but not recommend dose modifications for administration of gefitinib with CYP3A4 inhibitors for reasons discussed in Section 4 of this summary review. In addition, provided guidance on adjustment of dosing in patients taking proton pump inhibitors, H<sub>2</sub>-receptor antagonists, and antacids for reasons discussed in Section 4 of the summary review. Removed (b) (4)
  - Use in Specific Populations: Revised for conformance with PLLR; added recommendations for duration of contraceptive use in males and females of reproductive potential. Removed detailed information under Pediatric Use subsection and replaced with the statement that safety and effectiveness have not been established. (b) (4)
  - Overdosage: Edited for brevity.
  - Description: editorial changes and for inclusion of information as per regulations (21 CFR 201.57)
  - Clinical Pharmacology: edited for brevity and essential information, in accordance with FDA guidances on this section of product labeling.
  - Nonclinical Pharmacology/Toxicology: edited to described carcinogenicity study and reproductive toxicology studies in greater detail.
  - Clinical Studies: edited to include more detail on the clinical study design; information on patient demographics/tumor characteristics placed in text rather than tabular format. (b) (4)
  - Added description and results of the subset analysis of IPASS in patients with EGFR mutation-positive NSCLC as this data was relied upon as part of the totality of the evidence to support approval of gefitinib.
  - Storage/How Supplied: edited to include essential information.
  - Patient Counseling: Edited for conformance with FDA guidance on this section.
- Carton and immediate container label: All revisions requested by FDA to ensure consistency with regulations for carton and container labeling have been incorporated.
  - Patient labeling/Medication guide  
The clinical review team and the DRISK consultant determined that a Medication Guide was not required to ensure safe and effective use. Patient labeling submitted by AstraZeneca was revised to include simplified wording and clarify concepts to ensure that

the patient package insert (PPI) is consistent with the Prescribing Information (PI), remove unnecessary or redundant information, ensure that the PPI is free of promotional language, and to ensure that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

The recommendation for approval is based on the totality of the evidence, which includes demonstration of durable objective tumor responses in two trials, one prospectively conducted in a population with defined genetic tumor characteristics and one conducted in a subpopulation where tumor genetic characteristics were determined retrospectively. Although the subset analysis of the latter trial has the potential for selection bias in identification of the convenience sample, both trials are strengthened by the consistency of the response rate observed in both studies as determined by an independent assessment (BIRC). In addition, the data are consistent with the findings observed with other drugs in this class. While this does not eliminate the potential for bias, neither do these findings indicate that the results observed in the subset analysis of the IPASS trial are not representative and, therefore likely the result of biases.

The consideration for traditional approval was based on the totality of the evidence, which includes the consistent findings in IFUM and the subset on IPASS on durable response rates [BIRC-determined ORR of 50% (95% confidence intervals: 41, 59) with a median duration of response of 6.0 months (95% CI: 5.6, 11.1 months) and ORR of 67% (95% CI: 56, 77) with median duration of response of 9.6 months, respectively], the trend towards improved PFS in the ITT population enrolled in IPASS, and evidence that is biologically plausible that these findings are in fact driven by the subset of patients with EGFR mutation-positive NSCLC from the IPASS trial. The magnitude of the treatment effect observed in the subset of patients with EGFR mutation-positive NSCLC [HR of 0.54 (95% CI: 0.38, 0.79)] with a median PFS of 10.9 months for gefitinib compared to 7.4 months for carboplatin/paclitaxel corresponding to a 3.5-month increase in median PFS is clinically meaningful. Further, these results would have been predicted based on the observed ORR in both trials, based on FDA's analysis of patient-level data across 14 randomized trials evaluated with efficacy of drugs for the treatment of NSCLC<sup>1</sup> in which there was a strong association between PFS and ORR was strong ( $R^2 = 0.89$ ; 95% CI, 0.80 to 0.98).

The IPASS trial did not demonstrate an effect on overall survival, which is not surprising given the availability of other marketed EGFR tyrosine kinase inhibitors and likely use of these agents as second-line treatment. This observation (lack of survival effect) has also been observed in other trials of EGFR tyrosine kinase inhibitors for treatment of EGFR

mutation-positive NSCLC and has been attributed to second line treatment with an EGFR tyrosine kinase inhibitor for patients in the control arm.

The risks of gefitinib appear qualitatively similar to those of the currently approved EGFR tyrosine kinase inhibitors. The most frequent adverse reactions (incidence of >20% and greater than placebo) reported in 1126 gefitinib-treated patients enrolled in the ISEL trial, a randomized, placebo-controlled trial conducted in patients with NSCLC who were unable to tolerate or had experience disease progression on or within 90 days of receiving first- or second-line chemotherapy were: skin reactions (47%) and diarrhea (29%). Approximately 5% of gefitinib-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%). The most frequent fatal adverse reactions in gefitinib-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%). Across three large, randomized clinical trials, the most common serious adverse drug reactions of gefitinib are interstitial lung disease, hepatotoxicity, diarrhea, gastrointestinal perforation, and ocular toxicity. Based on the acceptance by the medical and patient community of a similar toxicity profile with currently marketed EGFR tyrosine kinase inhibitors, I conclude that these risks do not outweigh the benefits of gefitinib, which are also qualitatively similar to those observed with the currently marketed EGFR tyrosine kinase inhibitors.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
I concur with the review team that Risk Evaluation and Mitigation Strategies are not required to ensure safe and effective use of gefitinib for the indicated population.
- Recommendation for other Postmarketing Requirements and Commitments  
I concur with the review team that there are no studies needed to address outstanding safety issues under post-marketing requirements are required.

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<sup>1</sup> Blumenthal GB, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D, Tang S, Sridhara R, Keegan P, Pazdur R. Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non-Small-Cell Lung Cancer: US Food and Drug Administration Trial-Level and Patient-Level Analyses: J Clin Oncol March 20, 2015 vol. 33: 1008-1014.

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/s/  
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PATRICIA KEEGAN  
07/13/2015