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APPLICATION NUMBER:

206995Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206995
Priority or Standard	Standard
Submit Date(s)	September 17,2014
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Dickran Kazandjian, MD Gideon Blumenthal, MD (CDTL)
Review Completion Date	May 25, 2015
Established Name	Gefitinib
(Proposed) Trade Name	IRESSA
Therapeutic Class	tyrosine kinase inhibitor
Applicant	AstraZeneca
Formulation(s)	tablets for oral use
Dosing Regimen	250 mg daily
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
Intended Population(s)	see indication

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

On September 17, 2014, the Applicant submitted NDA 206995 for the re-introduction of gefitinib (IRESSA) for FDA approval. This submission included the clinical study reports and data sets for the clinical trials "IRESSA Follow-Up Measure" (IFUM) and IPASS to support efficacy and ISEL, INTEREST, and IPASS to support safety. IFUM was a single arm, open-label, study of gefitinib for the first-line treatment of Caucasian European patients with prospectively selected EGFR mutation positive non-small cell lung cancer (NSCLC). IPASS was a randomized study in Asian patients who were selected based on clinical features to receive first-line gefitinib or carboplatin/paclitaxel doublet therapy. Retrospective subgroup analysis was performed on this trial for patients who had EGFR mutation status evaluable. Given the results of IPASS and IFUM, the Applicant asserted that clinical benefit was verified and requested traditional approval of gefitinib in patients with EGFR mutation positive NSCLC.

Based on review of the clinical data, the clinical team recommends the approval of this NDA for the following indication:

IRESSA is indicated 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.*

The basis of this recommendation is the favorable benefit-risk profile from study IFUM, a multicenter, single arm, trial conducted exclusively in Europe in Caucasian patients evaluating gefitinib monotherapy in 106 patients with NSCLC containing epidermal growth factor receptor (EGFR) exon 19 deletions or L858R, L861Q, or G719X mutations. The primary outcome evaluated was objective response rate (ORR) as determined by a blinded independent radiology review (IRC). Key secondary endpoints included progression free survival (PFS) and Overall Survival (OS).

In IFUM, an investigator determined ORR of 70% (95%CI:60, 78) with 1.9% complete responses (CR) were observed in patients prospectively selected for EGFR positive sensitizing mutations. These responses were durable with a median duration of response (DoR) of 8.3 months (95%CI:7.6, 11.3). This was supported by the results of a blinded IRC with an ORR of 50% (95%CI:40, 60) and a median DoR of 6 months (5.6, 11.1).

The key supportive study for efficacy was "IRESSA Pan-Asia Study" (IPASS). This was a multicenter, randomized, open-label trial evaluating the first-line treatment of patients

with NSCLC who received gefitinib or carboplatin/paclitaxel conducted exclusively in Asia. Patients were selected based on clinical factors of non-smoking/ex-light smoking status, adenocarcinoma histology, and Asian ethnicity. In the intention to treat (ITT) of 1,217 patients enrolled, an improvement in investigator assessed PFS was observed in patients treated with gefitinib as compared to patients treated with carboplatin/paclitaxel (HR 0.74, 95% CI 0.65, 0.85). Of the 1,217 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 used in IFUM. Of these 261 patients, 186 (71%) had radiographic scans available for a retrospective assessment by an IRC. This subgroup analysis was the key supportive parameter to support the efficacy observed in the single arm IFUM trial. This subgroup of 261 patients suggested an improvement in PFS with gefitinib (n=132) compared to carboplatin/paclitaxel (n=129). A 3.5 month difference in median PFS (9.6 months [95%CI:8.0, 11.4] vs. 6.1 months [95%CI:5.5, 6.8]) and a 52% reduction in risk of progression (HR: 0.48 [95%CI:0.35, 0.64]; p=<0.0001)was observed in EGFR+ metastatic NSCLC patients treated with gefitinib compared to patients with chemotherapy.

In addition to the above trials, supporting data was also derived from two investigator-initiated randomized studies of gefitinib vs. doublet chemotherapy in first-line NSCLC (Study WJTOG3405 and Study NEJ002). Study WJTOG3405 (n=172) compared gefitinib to cisplatin/docetaxel and Study WJTOG3405 (n=228) compared it to carboplatin/paclitaxel chemotherapy and both studies were conducted Japan in prospectively selected patients with metastatic EGFR+ NSCLC. Clinical benefit was established in both these studies and the majority of the patients had tumors with exon 19 deletions or L858R substitution mutations in EGFR. In WJTOG3405, the median PFS for the gefitinib arm was 9.6 months (95%CI:8.4, 12.4) compared to 6.6 months (95%CI:5.9, 7.8) for the chemotherapy with a HR of 0.52 (95%CI:0.38, 0.72). In NEJ002, the median PFS for the gefitinib arm was 10.8 months compared to 5.4 months for the chemotherapy with a HR of 0.32 (95%CI:0.24, 0.44).

The safety profile for common adverse reactions related to gefitinib was based on the study “IRESSA survival evaluation in lung cancer” (ISEL). This was a double blinded, randomized study for the 2nd and 3rd line treatment of patients with unselected metastatic NSCLC who received gefitinib (n=1129) or placebo (n=563). Common adverse events occurring more frequently on the gefitinib arm included skin reactions and diarrhea. The most frequent fatal adverse reactions in patients treated with gefitinib were respiratory failure, pneumonia, and pulmonary embolism. The most frequent adverse reactions that led to discontinuation of gefitinib were nausea, vomiting, and diarrhea.

In addition to ISEL and IPASS, the safety database of the study “IRESSA NSCLC trial evaluating response and survival versus Taxotere” (INTEREST) was used to pool

adverse reactions across these trials to assess the frequency of serious and uncommon adverse drug reactions. INTEREST was a multicenter randomized study in patients with NSCLC not selected for EGFR mutational status who had previously progressed on front-line therapy in which patients received either gefitinib or docetaxel. Across these trials, less frequent but more severe adverse reactions occurring with gefitinib included hepatotoxicity, severe diarrhea, ocular disorders, interstitial lung disease (ILD) and gastrointestinal perforation.

1.2 Risk Benefit Assessment

Lung cancer is the leading cause of cancer-related death in the United States and world-wide and NSCLC represents 85% of these cases. Approximately 20-25% of patients with NSCLC of adenocarcinoma histology have tumors harboring mutations, small insertions, and deletions of the epidermal growth factor gene (EGFR), leading to constitutive activation of the EGFR tyrosine kinase. Gefitinib is a small molecule, tyrosine kinase inhibitor, which has the ability to inhibit the activity of select sensitive EGFR mutated tyrosine kinases, primarily exon 19 deletions and L858R mutations. Based on preliminary but potentially clinically meaningful results in ORR of ~15% in a refractory unselected patient population, gefitinib initially received accelerated approval in 2003 under subpart H as monotherapy for the treatment of patients with advanced NSCLC after failure of both platinum-based and docetaxel therapies (NDA 21399). Following accelerated approval of gefitinib in the US, AstraZeneca (AZ) initiated three randomized studies to confirm clinical benefit. These studies were “IRESSA vs Best Supportive Care Randomized Evaluation of Effect on Symptom Endpoint” (IBREESE), ISEL, and INTEREST. IBREESE was closed due to feasibility problems. The sponsor concluded that INTEREST suggested the non-inferiority of gefitinib compared to docetaxel (HR: 1.020; 95%CI:0.905, 1.150 [non-inferiority limit, HR 1.154 in HR terms]); median survival of 7.6 months with gefitinib versus 8.0 months with docetaxel. ISEL was conducted in an unselected population and failed to show a statistically significant improvement in OS versus placebo. The negative results from ISEL led to the subsequent withdrawal of the gefitinib NDA in the US in April 2012.

Subsequently, the understanding of the biology of EGFR mutated NSCLC improved, leading to a better understanding of the patient population most likely to derive benefit from EGFR TKIs in NSCLC, and to new trials in molecularly or clinically enriched patient populations. IPASS suggested that the EGFR mutation status of a patient’s tumor is predictive of gefitinib efficacy in Asian patients in the first-line setting. The approval of gefitinib in the European Union was based primarily on data from the IPASS study. Subsequently, the Applicant conducted IFUM to fulfil a commitment to the European Medicines Agency approval to conduct a follow-up study, to address the low number and percentage of tumor samples assessed for EGFR mutation status in non-Asian patients.

In IFUM, a clinically meaningful investigator determined ORR of 70% (95%CI:60, 78) with 1.9% CRs was observed in patients prospectively selected for EGFR sensitizing mutations. These responses were relatively durable with a median DoR of 8.3 months (95%CI:7.6, 11.3). This was supported by the results of the IRC which calculated an ORR of 50% (95%CI:40, 60) and a median DoR of 6 months (95%CI:5.6, 11.1). The discordance was largely attributed to the lack of RESIST evaluable disease in 17 patients per the IRC.

The results of IFUM were supported by the retrospective subgroup analysis of IPASS. This was a multicenter randomized trial conducted in Asia evaluating the first-line treatment of patients with NSCLC who received gefitinib or carboplatin/paclitaxel. status, adenocarcinoma histology, and Asian ethnicity. From the 1,217 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. Of these 261 patients, 186 (71%) had radiographic scans available for a retrospective assessment by a blinded IRC. The subgroup analysis was the key supportive result for efficacy in the current NDA. This subgroup of 261 patients suggested an improvement in PFS with gefitinib (n=132) compared to carboplatin/paclitaxel (n=129). A 3.5 month difference in median PFS (9.6 months [95%CI:8.0, 11.4] vs. 6.1 months [95%CI:5.5, 6.8]) and a 52% reduction in risk of progression (HR: 0.48 [95%CI:0.35, 0.64]; p=<0.0001)was observed in EGFR+ metastatic NSCLC patients treated with gefitinib compared to patients with chemotherapy. These results were supported by an IRC review.

Determination of the safety profile for gefitinib was based on the double blinded, randomized ISEL study for the 2nd and 3rd line treatment of patients with metastatic NSCLC who received best supportive care and gefitinib (n=1,129) or placebo (n=563). Common adverse events occurring more frequently (≥20%) on the gefitinib arm included: skin reactions (47% vs. 17%) and diarrhea (29% vs 10%). These common AEs were managed with supportive care and/or with dose interruptions. The most frequent fatal adverse reactions in were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%). Approximately 5% of IRESSA-treated patients discontinued treatment for adverse reactions of which the most frequent reasons were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

The safety databases of ISEL, IPASS, and INTEREST were pooled to evaluate serious and uncommon adverse drug reactions for patients treated with gefitinib (n=2,462). INTEREST was a multicenter randomized 2nd line treatment of NSCLC study in which patients received gefitinib or docetaxel. Across these trials, less frequent but more severe adverse reactions occurring with gefitinib included hepatotoxicity in which 11% of patients had increased alanine aminotransferase (ALT) and 2.7% of patients had increased bilirubin. Grade 3 or higher liver test abnormalities occurred in 5.1% (ALT)

0.7% (bilirubin) and death due to hepatic toxicity was 0.04%. Severe diarrhea (Grade 3 or 4) occurred in 3% of patients across these trials. Ocular disorders including keratitis, conjunctivitis, blephritis, dry eye, corneal erosion, and aberrant eyelash growth occurred in 7.0% of patients and the incidence of Grade 3 or 4 toxicity was 0.1%. ILD, including ILD-like adverse events (lung infiltration, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis, or abnormal chest X-ray) occurred in 1.5% of patients and of these, 0.8% were ≥ Grade 3, and 3 cases were fatal. Gastrointestinal perforation occurred in 3 of the 2,462 patients enrolled on these studies. Severe diarrhea Grade ≥3 occurred in 3% of patients.

Table 1: Benefit-Risk Analysis for gefitinib in the treatment of patients with metastatic EGFR mutation positive NSCLC (Source: FDA; Reviewer Table)

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

Abbreviations: NSCLC, non-small cell lung cancer; ORR, objective response rate; DOR, duration of response; ALT, alanine amino transferase

Reviewer Note: The risk-benefit evaluation for gefitinib was favorable. Gefitinib demonstrated a clinically meaningful ORR of 70% in patients who had sensitive EGFR mutations selected prospectively. The majority of EGFR mutations present were exon 19 deletions and L858R substitution mutations. Furthermore, these responses were durable with a median DoR of 8.3 months. The median survival in this study was > 19 months which surpasses historical standards for unselected metastatic NSCLC patients. This was supported by a retrospective subgroup analysis from IPASS in which patients with NSCLC containing EGFR sensitive mutations showed a clinically meaningful improvement in the primary endpoint of PFS, with a 3.5 month improvement in median PFS, and a 52% reduction in the relative risk of disease progression. Gefitinib-treated patients had a low frequency of serious adverse reactions such as ocular disorders, ILD and hepatotoxicity, and had common low grade reactions including skin reactions, diarrhea, decreased appetite, and eye disorders. In light of the benefit seen with gefitinib use in the appropriate patient population (EGFR mutation positive) the safety profile is deemed acceptable and less than or equal to other agents in this class.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide is required for marketing of gefitinib.

1.4 Recommendations for Postmarket Requirements and Commitments

No post marketing requirements or commitments are recommended for gefitinib.

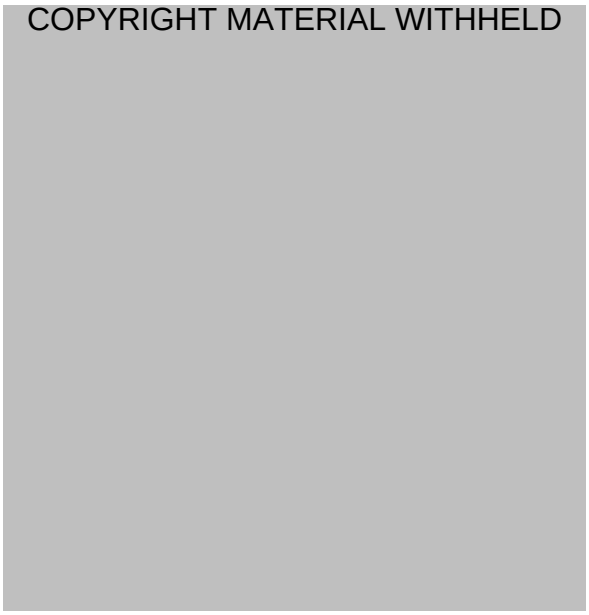
2 Introduction and Regulatory Background

Lung cancer is the second most common cancer after prostate cancer in men and breast cancer in women. Estimates for lung cancer in the United States for 2014 are 224,210 new cases, with 159,260 deaths, which accounts for 27% of all cancer deaths.[1] It is the leading cause of cancer death with more people dying of lung cancer than of colon, breast, and prostate cancers combined. The average age at the time of diagnosis is about 70 years.[1] Lung cancer incidence has been declining among men over the past 20 years and is now declining among women. Survival in lung cancer depends on the stage of disease at diagnosis.

Lung Cancer is broadly divided into two categories, non-small cell lung cancer (~85%) and small cell lung cancer. Non-small cell consists of two major histologic subtypes: adenocarcinoma and squamous cell carcinoma. The mainstay for curative treatment for early stage disease involves surgery and adjuvant platinum-based doublet chemotherapy, depending on the stage of disease. Five year survival for treated Stage I cancers are 50% and decline with advanced stages (Stage II: 30%; Stage III: 10%; Stage IV: 1%).[1] Overall, 5 year survival is a dismal 16%. There are a number of risk factors in the development of lung cancer thus far identified but the leading one is exposure to cigarette smoke.[2]

Cytotoxic chemotherapy is the backbone of treatment for patients with advanced NSCLC. Standard platinum doublets are the mainstay and result in median survivals of approximately 8 to 10 months. With the advent of targeted therapeutic approaches, a number of novel agents such as monoclonal antibodies, antibody directed conjugates and small molecule kinase inhibitors have been developed to target specific molecular aberrations. [3] One of the most studied "driver" pathways has been the EGFR and k-RAS pathways. EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib have been found to benefit mostly patients with drug sensitive EGFR mutations (present in about 20% of patients with adeno NSCLC).[4-8] There are a number of other genetic "driver mutations" which have recently been discovered. Crizotinib and ceritinib are FDA approved for patients with NSCLC whose tumors harbor ALK rearrangements (present in about 5% of adeno NSCLC).[9-13] Figure 1 below describes the most recent identified genetic lesions and possible drug targets for development.

Figure 1: Proportion of Specific Molecular Alterations in Adeno and Squamous Lung Carcinoma[14]



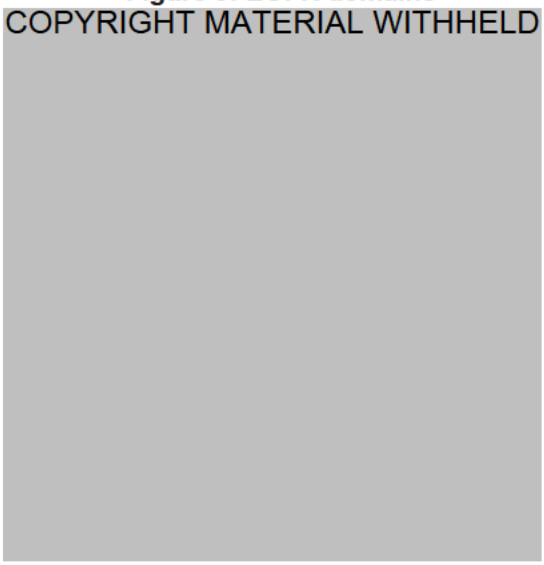
There have been a number of recent advances and drug approvals in lung adenocarcinoma with specific genetic abnormalities. These novel agents all appear to be associated with greater clinical benefit and less toxicity with each having a slightly different profile.

Epidermal growth factor receptor (EGFR), is a receptor tyrosine kinase which along with HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4) belong to the ErbB family. Its natural ligands (EGF, TGF-beta) bind and subsequently causes homo/hetero-dimerization and subsequent cascade activation involving the RAS, RAF, MEK, and MAPK pathways or the PI3K pathways. Ultimately, this leads to cell proliferation, survival, invasion, and metastasis (figure below).

Figure 2: ERB family of receptors[15]

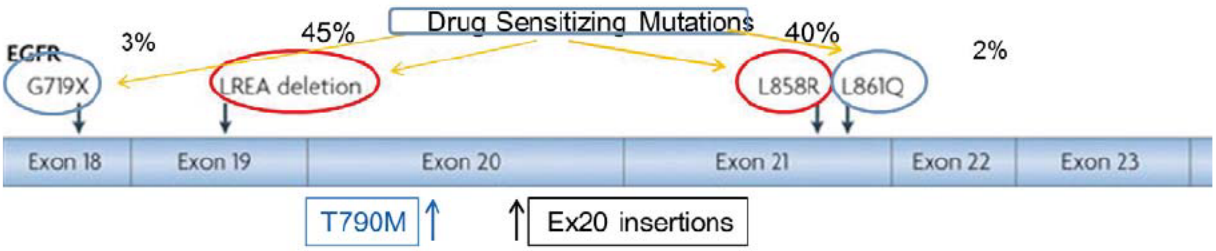
EGFR is a receptor tyrosine kinase. Mutations in the tyrosine kinase region might lead to constitutive activation.

Figure 3: EGFR domains[16]



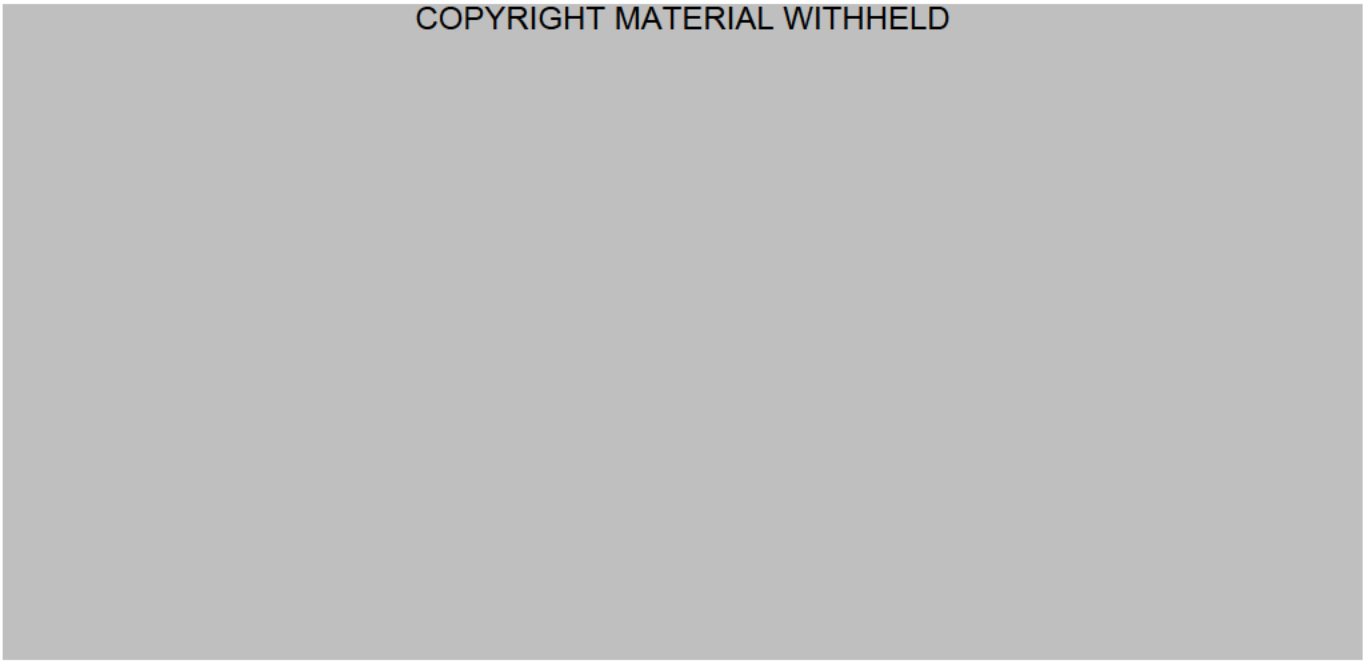
In the case of EGFR, there are primary drug sensitive and resistant mutations along with secondary resistance mutations. Activating mutations occur in the ATP binding pocket domain involving exons 18-21. Approximately 85% of all drug sensitive mutations involve the L858R mutation or small internal deletions of exon 19. Exon 20 insertions are in general resistant to EGFR TKIs. L861Q in exon 21 and G719X are less common and are thought to be intermediate in sensitivity to EGFR TKIs such as gefitinib.

Figure 4: Primary drug sensitive and resistant mutations



Secondary drug resistance occurs in a number of ways including mutations in EGFR (T790M) or activation of other pathways.

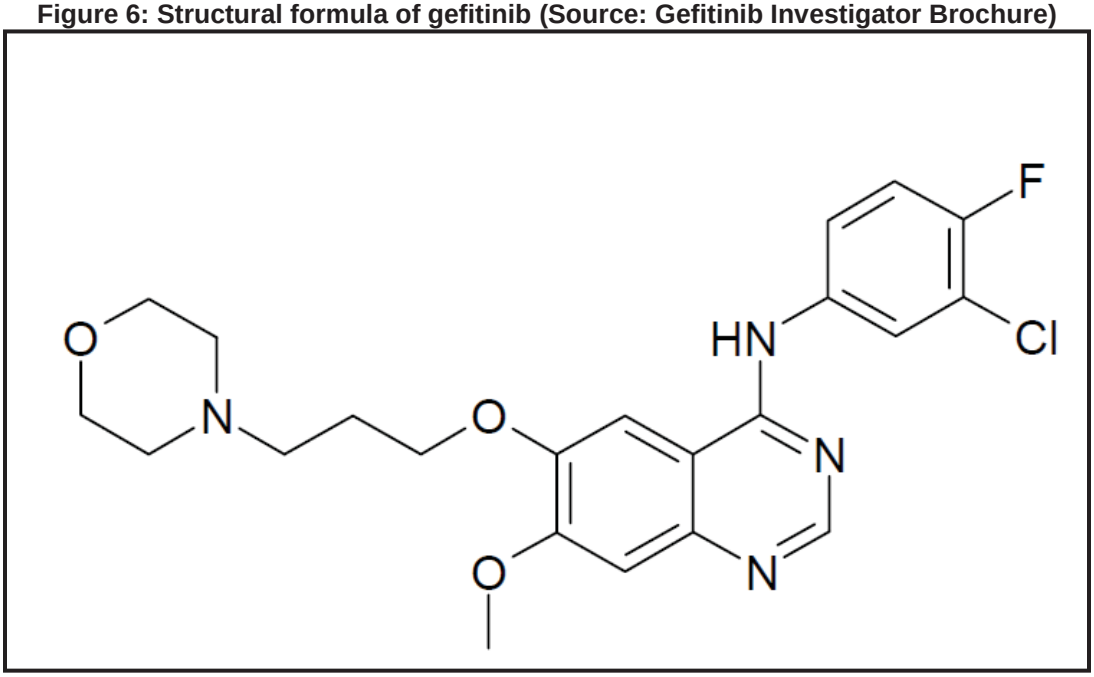
Figure 5: Secondary drug resistance[17]



2.1 Product Information

Gefitinib (IRESSA™, ZD1839) is a small molecule which is presented as a free base. Distinct features are the N-phenyl-4-quinazolinamine ("4-anilinoquinazoline") core structure with a combination of 3-(4-morpholinyl) propoxy and methoxy substituents at the 6 and 7 positions. It is an orally active, reversible, and selective inhibitor of EGFR TK (dissociation constants for gefitinib for the phosphorylated forms of the wild type EGFR is 140 nM and mutant EGFR is 10 nM. This receptor exists as a monomer that dimerizes following binding of a ligand to the extracellular portion of the EGFR. Selective inhibition by gefitinib of EGFR TK is thought to interrupt the mitogenic and survival signals responsible for cellular cancer processes.

Figure 6: Structural formula of gefitinib (Source: Gefitinib Investigator Brochure)



2.2 Tables of Currently Available Treatments for Proposed Indications

Figure 7: Available therapies for first-line treatment of EGFR+ lung adenocarcinoma (Source: FDA; Reviewer Table)

Drug	1st Line Treatment	Efficacy
Afatinib	First-line treatment for metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test	Afatinib vs pemetrexed/cisplatin with primary endpoint of PFS: mPFS: 11.1 (9.6-13.6) vs 6.9 (5.4-8.2) months; PFS HR: 0.58 (0.43-0.78) p<0.001; mOS: 28.1 (24.6-33.0) vs 28.2 (20.7-33.2) months; OS HR: 0.91 (0.66-1.25); p=0.55 ORR: 50.4% vs 19.1%
Bevacizumab	Unresectable, locally advanced, recurrent, or metastatic non–squamous NSCLC in combination with carboplatin and paclitaxel	Bevacizumab + carboplatin/paclitaxel vs carboplatin/paclitaxel with primary endpoint of OS: mOS: 12.3 vs 10.3 months; OS HR: 0.8 (0.68-0.94) p=0.013

Docetaxel	Unresectable, locally advanced or metastatic NSCLC in combination with cisplatin	Docetaxel + cisplatin vs vinorelbine + cisplatin with primary endpoint OS:
		mOS: 10.9 vs 10.0 months; OS HR: 0.88 (0.74-1.06) p=0.122;
		mTTP: 21.4 (19.3-24.6) vs 22.1 (18.1-25.6) weeks; p=NS;
		ORR: 31.6% (26.5-36.8) vs 24.4% (19.8-29.2) p=NS

Erlotinib	Metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test	Erlotinib vs platinum doublet with primary endpoint of PFS: mPFS: 10.4 (8.7-12.9) vs 5.2 (4.6-6.0) months; PFS HR: 0.34 (0.23-0.49) p<0.001; mOS: 22.9 (17.0-26.8) vs 19.5 (17.3-28.4) months; OS HR: 0.93 (0.64-1.35); ORR: 65% (54.1-75.1) vs 19.1% (9.0-25.3)
Gemcitabine	Inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC in combination with cisplatin	1. Gemcitabine + cisplatin vs cisplatin with primary endpoint OS: mOS: 9.0 (8.2-11.0) vs 7.6 (6.6-8.8) months p=0.008; mTTP: 5.2 (4.2-5.7) vs 3.7 (3.0-4.3) months p=0.009 ORR: 26% vs 10% p<0.0001 2. Gemcitabine + cisplatin vs etoposide + cisplatin with primary endpoint OS:

		mOS: 8.7 vs 7.0 months p=0.18 mTTP: 5.0 vs 4.1 months p=0.015; ORR: 33% vs 14% p=0.01
[redacted]		(b) (4)
Paclitaxel	In NSCLC patients in combination with cisplatin who are not candidates for potentially curative surgery and/or radiation therapy	Paclitaxel + cisplatin vs etoposide: mOS: 9.3 vs 7.4 months p=0.08; mTTP: 4.3 vs 4.9 months p=0.004 ORR: 25% vs 12% p<0.001
Pemetrexed	Locally advanced or metastatic **non-squamous NSCLC** patients in combination with cisplatin	Pemetrexed + cisplatin vs gemcitabine + cisplatin with primary endpoint OS: mOS: 10.3 (9.8-11.2) vs 10.3 (9.6-10.9) months; OS HR: 0.94 (0.84-1.05); mPFS: 4.8 (4.6-5.3) vs 5.1 (4.6-5.5) months; ORR: 27.1% (24.2-30.1) vs 10% (21.8-27.6)
Vinorelbine	Unresectable, advanced NSCLC as a single agent or in combination with cisplatin for treatment of ambulatory patients	1. Vinorelbine + cisplatin vs cisplatin with primary endpoint OS: mOS: 7.8 (6.9-9.6) vs 6.2 (5.4-7.7) months p=0.01; ORR: 19% (14-25) vs 8% (5-13) p<0.001 2. Vinorelbine + cisplatin vs vindesine + cisplatin with primary endpoint OS: mOS: 9.2 (7.4-11.1) vs 7.4 (6.1-9.1) months p=0.087 ORR: 28% (22-35) vs 19% (14-25) p=0.03

Figure 8: Available therapies after first-line doublet chemotherapy for treatment of EGFR+ lung adenocarcinoma (Source: FDA; Reviewer Table)

Drug	NSCLC Refractory Indication	Efficacy
Docetaxel	Locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy	1. Docetaxel vs ifosfamide or vinorelbine with primary endpoint OS: mOS: 5.7 (5.1-7.1) vs 5.6 (4.4-7.9) months; OS HR: 0.82 (0.63-1.06) p=0.13; mTTP: 8.3 (7.0-11.7) vs 7.6 (6.7-10.1) weeks ; ORR: 5.7% (2.3-11.3) vs 0.8% (0.0-4.5) 2. Docetaxel vs best supportive care with primary endpoint OS: mOS: 7.5 (5.5-12.8) vs 4.6 (3.7-6.1) months; OS HR: 0.56 (0.35-0.88); p=0.01 mTTP: 12.3 (9.0-18.3) vs 7.0 (6.0-9.3) weeks ; ORR: 5.5% (1.1-15.1) vs n/a
Erlotinib	Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen	Erlotinib vs Placebo with primary endpoint OS : mOS: 6.7 vs 4.7 months; OS HR: 0.73 (0.61-0.86) p<0.001; mPFS: 9.9 vs 7.9 weeks; PFS HR: 0.59 (0.50-0.70) p<0.001; ORR: 8.9% vs 0.9% p<0.001
Pemetrexed	Locally advanced or metastatic **non-squamous NSCLC** after prior chemotherapy	Pemetrexed vs Docetaxel non-inferiority study with primary endpoint of OS: mOS: 8.3 (7.0-9.4) vs 7.9 (6.3-9.2) months; OS HR: 0.99 (0.82-1.20); mPFS: 2.9 (2.4-3.1) vs 2.9 (2.7-3.4) months; PFS HR: 0.97 (0.82-1.16); ORR: 8.5% (5.2-11.7) vs 8.3% (5.1-11.5)
Ramucirumab + Docetaxel	In combination with docetaxel for metastatic NSCLC with disease progression on or after platinum-based chemotherapy.	Docetaxel + Ramucirumab vs Docetaxel + placebo with primary endpoint OS: mOS: 10.5 (9.5-11.2) vs 9.1(8.4-10.0) months; OS HR: 0.86 (0.75-0.98) p=0.024; mPFS: 4.5 (4.2-5.4) vs 3.0 (2.8-3.9) months; PFS HR: 0.76 (0.68-0.86) p<0.001; ORR: 23% (20-26) vs 14% (11-17) p<0.001

2.3 Availability of Proposed Active Ingredient in the United States

The drug product, IRESSA 250mg tablets, is well established and has been marketed in over 90 countries since 2002. It was voluntarily withdrawn from the US in 2012. The key changes since 2011 relating to drug substance are:

1. Replacement of AstraZeneca Macclesfield, UK as site of gefitinib drug substance manufacture by (b) (4). The manufacturing process and controls remain unchanged.
2. Changes to the container/closure system (b) (4) for drug substance.
3. Inclusion of an additional supplier of the starting material (b) (4). The specification remains unchanged.

The key changes since 2011 relating to drug product are:

1. Removal of (b) (4) at AstraZeneca Macclesfield, UK for drug product manufacture of commercial supplies.

2.4 Important Safety Issues With Consideration to Related Drugs

Currently, the two most related drugs that are marketed are erlotinib and afatinib. The major clinically significant adverse drug reactions with these EGFR TK inhibitors include:

- Interstitial Lung Disease (erlotinib & afatinib)
- Renal Failure (erlotinib)
- Hepatotoxicity with or without Hepatic Impairment (erlotinib & afatinib)
- Gastrointestinal Perforation (erlotinib)
- Bullous and Exfoliative Skin Disorders (erlotinib & afatinib)
- Myocardial Infarction/Ischemia (erlotinib)
- Cerebrovascular Accident (erlotinib)
- Microangiopathic Hemolytic Anemia with Thrombocytopenia (erlotinib)
- Ocular Disorders (erlotinib & afatinib)
- Diarrhea (afatinib)

Common adverse events include:

- Rash (erlotinib & afatinib)
- Diarrhea (erlotinib & afatinib)
- Cough (erlotinib)
- Dyspnea (erlotinib)
- Stomatitis (afatinib)
- Dry Skin (afatinib)

- Paronychia (afatinib)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In November 1997, the original IND (54576) was submitted for the investigation of gefitinib in the treatment of patients with varying cancer types. A rolling submission under NDA 21399 occurred between July 2001 and Aug 2002 and in May 2003, gefitinib received accelerated approval under 21 CFR 314, subpart H as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. In June 2005, a supplement was approved providing labeling restrictions to use only in patients already receiving and benefiting from gefitinib therapy. After further discussions regarding failure to confirm clinical benefit under 21 CFR 314, subpart H, gefitinib was voluntary withdrawn from the market in April 2012.

In December 2013, IND 120992 was opened with a request for a Pre-NDA meeting to discuss the new drug application for IRESSA for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test. (b) (4) n March 2014, a Type B Pre-NDA meeting was conducted to discuss the content and format of a new drug application for IRESSA as a first-line treatment of patients with EGFR mutation (b) (4) metastatic NSCLC. In May 2014, FDA agreed that a 120-day safety report was not needed. In August 2014, gefitinib received orphan drug designation. In September 2014, this current submission was received.

2.6 Other Relevant Background Information

Gefitinib had initially received accelerated approval in 2003 but was subsequently voluntarily withdrawn. The nature of the withdrawal involved clinical trial designs which were not optimal in selecting the appropriate patients likely to benefit. Specifically, earlier, the science behind the optimal predictive biomarker for EGFR TKIs in NSCLC was unclear. Around 2004, scientists investigating tumor specimens from exceptional gefitinib responders discovered that somatic mutations in the EGFR kinase domain was oncogenic and inhibition of this pathway leads to apoptosis of cancer cells. Thus, somatic, sensitizing and activating mutations in EGFR are predictive of response to EGFR TKIs.

Gefitinib was initially developed in heavily pre-treated, unselected NSCLC patients. Early clinical data from the IDEAL I (Fukuoka et al 2003) and II (Kris et al 2002) studies, assessed 2 doses of gefitinib, 250 mg and 500 mg. From these studies, 250 mg was identified out of these two doses as the biological effective dose for NSCLC. The ORR

was 18.4% in IDEAL I and 11.8% in IDEAL II and these ORRs did not differ based on the dose used. Given the efficacy signal in IDEAL studies; gefitinib 250 mg (once daily) was approved initially in Japan in 2002 and approved in the US in May 2003. Following Subpart H approval of gefitinib in the US, AstraZeneca initiated 3 confirmatory randomized Phase 3 studies as US post-approval commitment studies:

1. IRESSA vs Best Supportive Care Randomized Evaluation of Effect on Symptom Endpoint (IBREESE; D7913C00710),
    a. The IBREESE study was closed due to feasibility issues.
2. IRESSA Survival Evaluation in Lung Cancer (ISEL; D7913C00709),
    a. The ISEL study was conducted in unselected, second- and third-line patients versus placebo with a primary endpoint of OS. ISEL failed to show a statistically significant improvement in OS versus placebo (HR: 0.89; 95% CI: (b) (4) p= (b) (4)). In ISEL, for the subgroup of never smokers, the HR for OS was 0.67 (95% CI: 0.49, (b) (4) p= (b) (4)) and for the subgroup of patients of Asian origin the HR for OS was 0.66 (95% CI: 0.48, 0.91; p= (b) (4))
3. IRESSA Non-small cell lung cancer Trial Evaluating Response and Survival against Taxotere (INTEREST; D791GC0001).
    a. The INTEREST study was conducted in an unselected second-line setting versus docetaxel with a primary endpoint of OS. The INTEREST study demonstrated non-inferiority for gefitinib versus docetaxel (b) (4) and that gefitinib was better tolerated than docetaxel.

In early clinical development in unselected patient populations it became apparent that gefitinib demonstrated better efficacy in patients with tumors of adenocarcinoma histology, never smokers and Asian patients than those patients with tumors of non-adenocarcinoma histology, smokers and Caucasians. At that time the association of these clinical phenotypes with EGFR genotypes was unknown. During the design of Study IPASS, a decision was made to select patients based on the clinical phenotype and analysis of tumor samples for EGFR status was an exploratory objective.

Per the sponsor, IPASS met its primary objective of showing the non-inferiority of gefitinib and also showed its superiority, compared with carboplatin–paclitaxel, with respect to PFS in the clinically selected overall patient population (ITT population; n=1217; HR: 0.74; 95% CI: 0.65, 0.85; p<0.0001). A relationship between EGFR mutation status and treatment in terms of PFS was observed during pre-defined subgroup analyses.

Subsequently, 2 independent randomized Phase 3 studies (WJTOG3405 [Mitsudomi et al 2010 and Mitsudomi et al 2012] and NEJ002 [Maemondo et al 2010 and Inoue et al 2013]) of gefitinib versus chemotherapy have been reported in Japanese patients.

These 2 studies prospectively enrolled only patients with EGFR mutation-positive NSCLC in the first- line setting vs doublet chemotherapy. WJTOG3405 study showed a longer PFS for patients treated with gefitinib compared with cisplatin/docetaxel (median PFS 9.6 months versus 6.6 months; HR: 0.520; 95% CI: 0.378, 0.715; p<0.0001). The NEJ002 study showed patients treated with gefitinib had significantly longer PFS compared with carboplatin/paclitaxel (median PFS 10.8 months versus 5.4 months; HR: 0.322; 95% CI: 0.236, 0.438; p<0.001). Results from both studies supported the importance of the EGFR mutation biomarker in selection of patients.

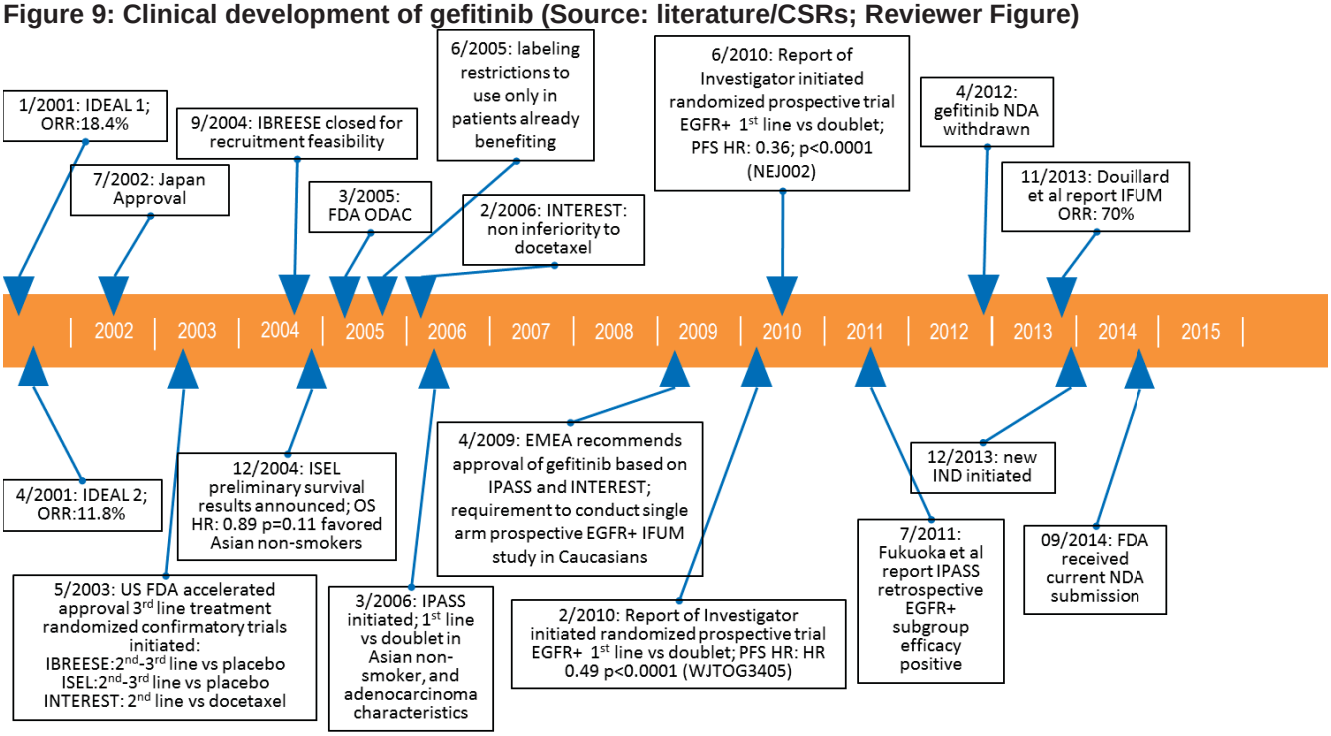
The European Medicines Agency (EMA) requested a follow-up study (as part of their conditional approval) to confirm the effectiveness of gefitinib in Caucasian patients. The IFUM study was a multicenter, single-arm study to characterize the efficacy and safety of gefitinib 250 mg (once daily) as first-line treatment in Caucasian patients with EGFR mutation-positive advanced NSCLC. The study demonstrated the efficacy, tolerability, and safety of gefitinib in Caucasian patients with EGFR mutation-positive advanced NSCLC.

AstraZeneca (AZ) is collaborating with Qiagen to provide a companion diagnostic to support a gefitinib indication for the first-line treatment of NSCLC patients with Exon 19 deletions or the Exon 21 substitution (L858R) mutation as detected by an FDA-approved test. Qiagen has submitted a supplementary PMA for the therascreen® EGFR RGQ PCR Kit (EGFR Kit), as a companion diagnostic.

Gefitinib is currently approved in 91 countries worldwide, including all EU member states, for the treatment of advanced NSCLC. Since the data from IPASS became available (2009), many of the marketing authorizations for gefitinib have been amended to indicate gefitinib only for use in patients with activating mutations of EGFR TK.

The sponsor has resubmitted gefitinib for US approval based on the totality of evidence based on the above studies. In regard to this review, the IFUM study is considered pivotal and the IPASS as supportive for efficacy. While safety was evaluated based on the randomized trials namely, ISEL, IPASS, and INTEREST.

Figure 9: Clinical development of gefitinib (Source: literature/CSRs; Reviewer Figure)



3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission by the Applicant contains all the components of e-CTD. In general, it was not well organized, however, it was considered adequate enough for substantive review of the contents. Regarding the pivotal study IFUM, 45 medical sites enrolled patients in 13 countries.

Figure 10: Distribution of patient between enrolling sites in IFUM (Source: IFUM Dataset; Reviewer Figure)

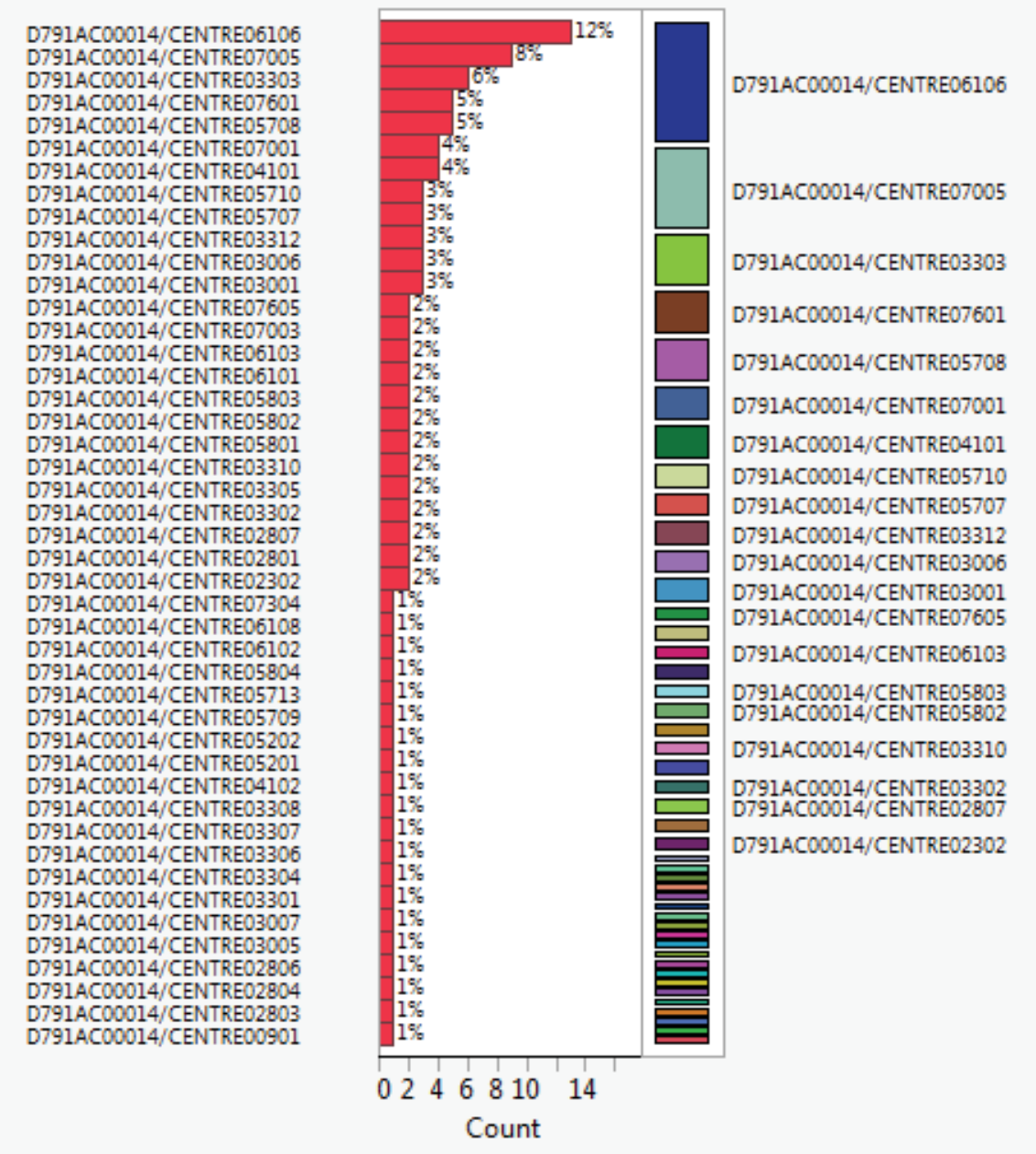
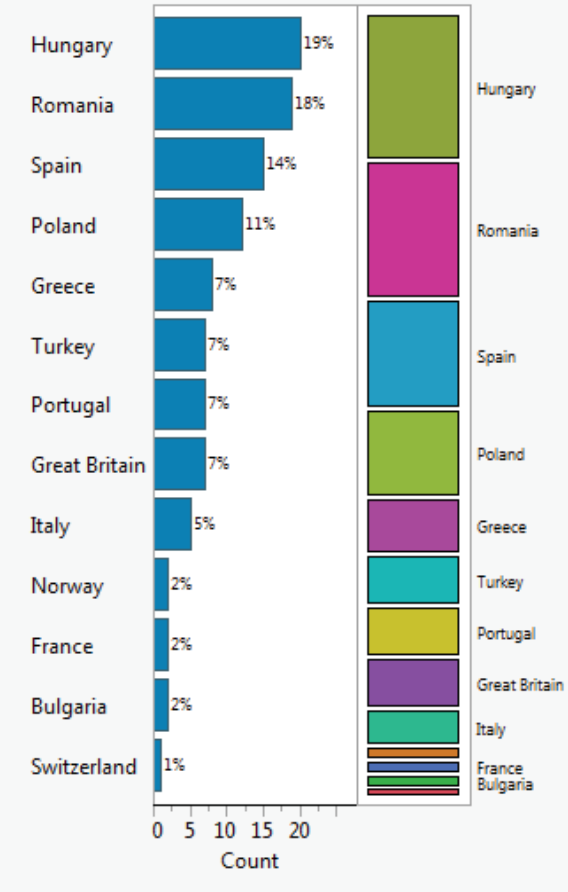


Figure 11: Distribution of patient enrollment per country for IFUM (Source: IFUM Dataset; Reviewer Figure)



To evaluate for any potential differences in clinical sites and countries, FDA conducted subgroup analysis of the primary endpoint, investigator determined ORR, to exclude significant outlying center or nation.

Figure 12: Countries colored by enrolled patient frequency in IFUM (Source: IFUM Dataset; Reviewer Figure)

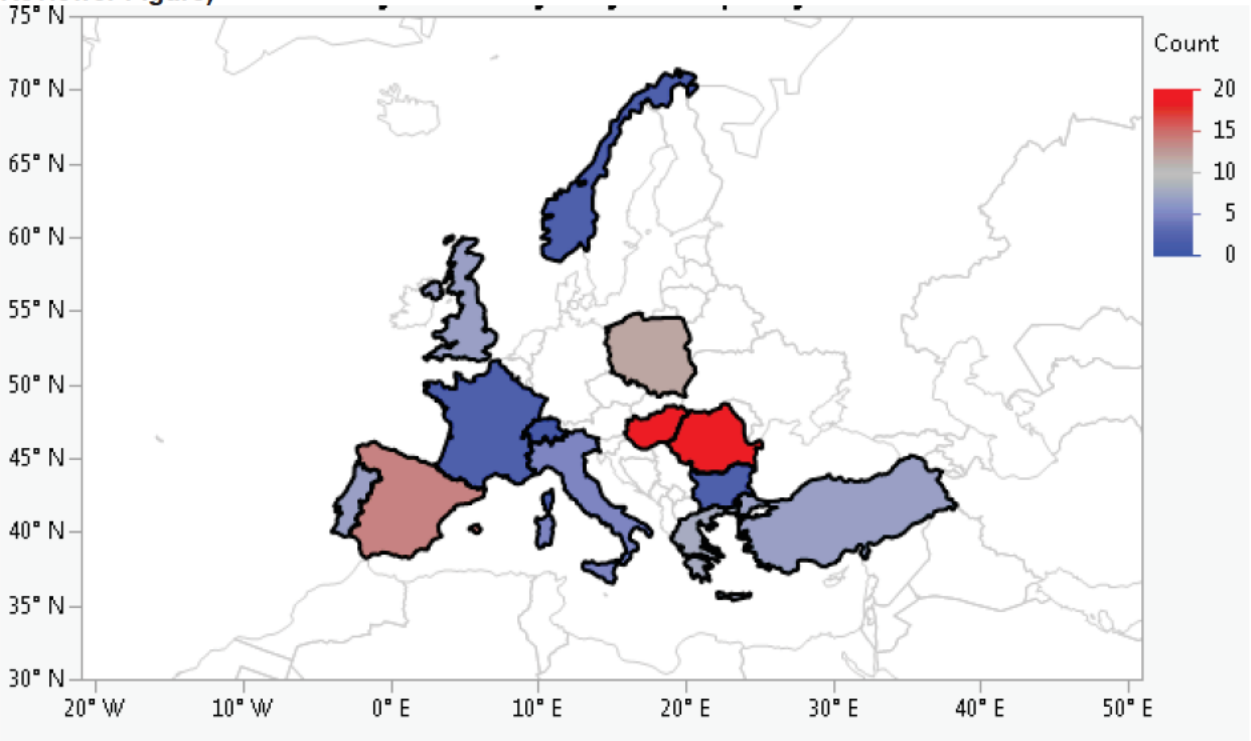


Table 2: Number of patients and respective ORR for all countries enrolling >2% of the total patients for IFUM (Source: IFUM Dataset; Reviewer Table)

Country	Number of Patients Enrolled ITT	Country specific ORR (95%CI)
Entire Study	**n=106**	**69.8% (60.5, 77.7)**
Hungary	20	70.0%
Romania	19	68.4%
Spain	14	71.4%
Poland	12	50.0%
Greece	8	87.5%
Great Britain	7	71.4%
Portugal	7	85.7%
Turkey	7	71.4%
Italy	5	80%

Reviewer Note: Italian, Portuguese, and Greek sites appeared to have higher ORR. An analysis excluding these countries showed that the ORR was 66.3%. This is reasonably similar to the ITT ORR.

Table 3: Five highest enrolling sites, ORR of individual sites, and ORR if site is excluded in IFUM (Source: IFUM Dataset; Reviewer Table)

Site Number	Country	Number of Patients Enrolled	Site specific ORR	Study ORR excluding site ORR (95%CI)
Entire Study		**106**	**69.8% (60.5, 77.7)**	
6106	Romania	13	69%	69.9% (60.0, 78.5)
7005	Spain	8	63%	70.4% (60.7, 78.5)
3303	Hungary	6	50%	71.0% (61.5, 79.0)
7601	Turkey	5	80%	69.3% (59.7, 77.5)
5708	Poland	5	60%	70.3% (60.8, 78.3)

Reviewer Note: Although the Turkish site shows a higher than expected response rate, this negligibly affects the overall response rate for the trial.

3.2 Compliance with Good Clinical Practices

The Applicant states that its procedures, internal quality control measures and audit programs provide reassurance that the clinical study program conducted by the Applicant was carried out in accordance with Good Clinical Practice, as documented by the International Conference on Harmonization (ICH). The WJTOG3405 study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Japanese Ministry of Health, Labor and Welfare Ethical Guidelines for Clinical Studies.

Per the Applicant, quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, were directed towards all aspects of the clinical study process and its associated documentation.

The Office of Scientific Investigation performed an inspection of the IRC/CRO (b) (4) (b) (4) Please see their review for details. In brief, their review concluded that 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 Central Imaging Vendor, (b) (4) is No Action Indicated (NAI). The inspection focused primarily on assessing the integrity of the tumor response and disease

progression source records for data generated by the BICR Vendor, for IFUM, and comparing those source data to the data listings submitted to the application. The inspection also included a review of the firm's organization and personnel, staff and contract staff qualification and training, correspondence, quality assurance, data collection and handling, computer system validation, standard operating procedures review and adherence, and BICR Charter adherence. Records and procedures were adequate, and generally well organized. The primary efficacy endpoint support data, tumor response, generated by the BICR Contractor and submitted to NDA 206995 were verifiable for six clinical sites. For all six sites, all subjects' image readings performed by the CRO radiologist were verified against the data listings submitted to the application; 36 subject endpoints and 239 subject time points. The CRO generated a total of 104 subject endpoints and 757 subject time points. Also, there was no evidence of BICR non-compliance with the Charter. No Form FDA 483 was issued. The data from this contractor, (b) (4), who performed the function of the BICR/Central Imaging Vendor for IFUM appear reliable and may be used in support of the respective indication.

3.3 Financial Disclosures

The Applicant provided a debarment certification stating that in connection with this NDA, the services of any person in any capacity debarred under section 306 (a) or (b) was not utilized.

For IFUM, the Applicant provided form 3454 covering financial arrangements which may affect study results. This included 272 clinical investigators with their institution and country listed who had no information to disclose. In addition, a due diligence document and form was provided in Module 1.3 of the eCTD stating that the Applicant in due diligence was unable to collect financial disclosures from 15 investigators. None of these investigators enrolled more than 2 patients, and thus are not likely to have altered global study results. The reasons for not being able to collect the documents were given for each investigator.

For IPASS, the Applicant provided form 3454 covering financial arrangements which included 607 clinical investigators with their institution and country listed who had no information to disclose. Two investigators reported interests:

1. (b) (6) responded positively for financial arrangements whereby the value of the compensation could be influenced by the outcome of the trial. According to the text of his Financial Disclosure Form, he received compensation for giving lectures but had no stock. "The monetary amount of rewards was not reported due to the accounting system of the study site, but there reportedly was no significant growth before and after participating this study. (b) (6)

is listed as a participating sub-investigator for IPASS. Center [redacted] enrolled and randomized [redacted] subjects out of a total of [redacted] subjects for the study. the Applicant states that the low number of evaluable subjects recruited at Centre [redacted] where [redacted] is associated should prevent any bias that possibly could affect the outcome of the study.

2. [redacted] and therefore acts as one of two [redacted] Committee co-chairs, for which he is reimbursed for his time. In addition he is the PI at one site – site [redacted] Per the Applicant, at site [redacted] was supported by [redacted] who assisted in all aspects of the trial, from patient selection through to assessment of tumor response by [redacted]. In addition, per the Applicant, all critical data were source data verified by AstraZeneca personnel. Center [redacted] enrolled [redacted] subjects out of a total of [redacted] subjects for the study and randomized [redacted] subjects out of a total of [redacted] The Applicant states that the study design [redacted] ecruited by [redacted] should prevent any bias that possibly could affect the outcome of the trial.

In addition, a due diligence document and form was provided in Module 1.3 of the eCTD stating that the Applicant in due diligence was unable to collect financial disclosure from 3 investigators. The reasons for not being able to collect the documents were given for each investigator.

Reviewer Note: In summary, financial interests are unlikely to have affected the results of the key efficacy studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC review for full details. The drug substance is manufactured at the contract sites [redacted] The [redacted] facility has not been inspected by FDA since 2008. The drug product is manufactured at the AstraZeneca UK Ltd. site in the UK.

4.2 Clinical Microbiology

n/a

4.3 Preclinical Pharmacology/Toxicology

Please see preclinical pharmacology review for further details. Gefitinib is a tyrosine kinase inhibitor with selective activity certain EGFR mutations over wild-type EGFR. In in vitro assays, gefitinib also inhibited IGF and PDGF-mediated signaling. All nonclinical toxicology studies required to support the approval of gefitinib were previously reviewed under NDA21399. The Applicant has submitted limited new pharmacology studies to support the mechanism of action of gefitinib in the intended patient population. The Applicant presented data from the scientific literature identifying and characterizing sensitizing mutations in the intracellular kinase domain of EGFR in tumor tissue samples obtained from a subset of patients with NSCLC who showed marked responses to gefitinib. The most common of these mutations were a set of deletions within exon 19 ('Ex19 del') and a point mutation of exon 21 ('L858R').

The submitted data also indicate that inhibition of L858R EGFR phosphorylation inhibited the phosphorylation of known downstream targets of EGFR such as 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 at gefitinib doses of 12.5 and 50 mg/kg, tumor volumes in A549-bearing nude mice were inhibited by 44% and 76%, respectively. Preclinical pharmacology had no outstanding issues that would prevent the approval of gefitinib for the treatment of patients with (b) (4) metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R (b) (4) substitution mutations as detected by an FDA-approved test.

4.4 Clinical Pharmacology

Please see clinical pharmacology for full details.

4.4.1 Mechanism of Action

Gefitinib is an inhibitor of EGFR tyrosine kinase proposed for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

4.4.2 Pharmacodynamics

The efficacy and safety of gefitinib were assessed in the IFUM and IPASS trials with a 250 mg daily dose regimen. In IFUM, the primary endpoint of ORR was 69.8% (74 of 106 patients), which was similar to the ORR observed in the EGFR mutation-positive subgroup from IPASS (71.2%), in which Asian patients with NSCLC were enrolled without regard to EGFR mutation status. A flat exposure-response (E-R) relationship for efficacy (response rate) was observed in the IFUM study. In the "IRESSA Dose

Evaluation in Advanced Lung cancer" (IDEAL) I and II studies, a doubling of gefitinib dose (500 mg daily vs. 250 mg daily) resulted in an increase in treatment-related toxicities. In patients receiving 500 mg daily of gefitinib, dose reductions due to toxicity ranged from 8.8-10.4% compared to less than 1% in patients receiving 250 mg daily. An E-R analysis based on an observational study (Study V- 15-33) in Japanese NSCLC patients indicated that a higher risk of ILD may be associated with higher exposure to gefitinib.

4.4.3 Pharmacokinetics

In a study of subjects with hepatic impairment due to cirrhosis, exposure to gefitinib was approximately 1.4-, 3.6-, and 2.7-fold higher in subjects with mild, moderate, and severe hepatic impairment compared to subjects with normal hepatic function. In a study in healthy subjects, cytochrome P450 (CYP) 2D6 poor metabolizers (PMs) had 2.1-fold higher exposure to gefitinib compared to CYP2D6 extensive metabolizers (EMs). However, dose adjustment is not recommended in patients with hepatic impairment or in CYP2D6 poor metabolizers because exposures in each group overlapped in these studies and dose reduction due to toxicity was relatively low in the Phase 2 studies in NSCLC patients when the dose was doubled. Clinical pharmacology recommended caution when using gefitinib in patients with hepatic impairment due to cirrhosis or CYP2D6 poor metabolizers due to the potential increase of gefitinib exposure in these patients. However, PK parameters in CYP2D6 ultra-rapid metabolizers remain uncharacterized. Clinical pharmacology recommended that the applicant conduct a study to characterize the pharmacokinetic properties of gefitinib in CYP2D6 ultra metabolizers, who may be at risk for treatment failure because of low exposure. This recommendation will be submitted via IND 120992.

5 Sources of Clinical Data

This NDA includes two clinical study reports and data sets which will be used to support efficacy (IFUM and IPASS). IFUM for this review will be considered the pivotal phase 2 single arm study conducted in patients prospectively found to have metastatic EGFR+ NSCLC requiring first-line therapy. IPASS is a supportive first-line randomized study in Asian patients who were selected based on clinical features. A subset of these patients underwent retrospective testing for EGFR mutation status

Safety of this drug will be mainly evaluated by the submitted study results and data sets for study ISEL, a randomized placebo controlled second-line study with no EGFR selection. Data from this trial along with IPASS and INTEREST was used to determine the incidence of rare but serious drug reactions.

5.1 Tables of Studies/Clinical Trials

Table 4: Studies used in the submission (Source: NDA206995 Summary of Clinical Efficacy; Reviewer Table)

Study	Design	Cancer	N	Efficacy	Comments
IFUM Pivotal	Phase 2, single arm, Caucasians prospectively selected based on EGFR mutation	EGFR+ NSCLC 1st line	106	ORR: 69.8% mPFS: 9.7m mOS: 19.2 m	IRC determined: ORR: 50% Prospective testing in Caucasians (CSRs and data sets)
IPASS Key Supportive	Phase 3, randomized, Carboplatin/ Paclitaxel In Asian patients	1st line NSCLC Selected: Sex Light Smoking Adenocarcinoma	261 of 1217	PFS HR: 0.48 mPFS: 9.5m vs 6.3m ORR: 71.2% vs.47.3% OS HR: 1.0 mOS: 21.6m vs. 21.9m	Retrospective convenience sample in Asians Supportive for efficacy and safety (CSRs and data sets)
ISEL & INTEREST	Phase 3 vs Placebo or Docetaxel	Unselected 2nd/3rd line NSCLC	World-wide study in unselected patients Submitted for Safety Both did not meet their primary endpoint (CSRs and data sets)		

5.2 Review Strategy

The clinical review of efficacy is based on the clinical study report for the pivotal study IFUM and supplemented with the supportive retrospective analysis of IPASS. The review of safety for common adverse events is based on the placebo controlled ISEL study while the review of significant adverse events is based on the pooled analysis of studies IPASS, ISEL, and INTEREST. The clinical study reports, supportive analyses

and risk:benefit assessment submitted by the applicant were reviewed. Key safety and efficacy datasets were re-analyzed by the clinical and statistical reviewers. The efficacy and safety review was conducted by Dr. Dickran Kazandjian and reviewed by Dr. Gideon Blumenthal. A statistical review was conducted by Dr. Vivian Yuan. Among the items reviewed were the case report forms, selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant. The reliability of the data were assessed based on information obtained from the OSI site visit of the clinical research organization (CRO), conflict of interest data, protocol deviations and via random cross-validation of datasets with CRF forms. Sensitivity analyses and subgroup analyses were performed as necessary.

5.3 Discussion of Individual Studies/Clinical Trials

STUDY IFUM:

The IRESSA Follow-Up Measure study (IFUM) was designed to characterize the efficacy and safety of gefitinib as first-line treatment in Caucasian patients with activating sensitizing EGFR mutation-positive (EGFR M+) locally advanced or metastatic non-small cell lung cancer (NSCLC). This NDA submission is primarily supported by the results of this industry-sponsored trial titled:

An Open-Label, Multicenter, Single-Arm Study to Characterize the Efficacy, Safety, and Tolerability of Gefitinib 250 mg (IRESSA) as First-Line Treatment in Caucasian Patients Who Have Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Design and treatment plan:

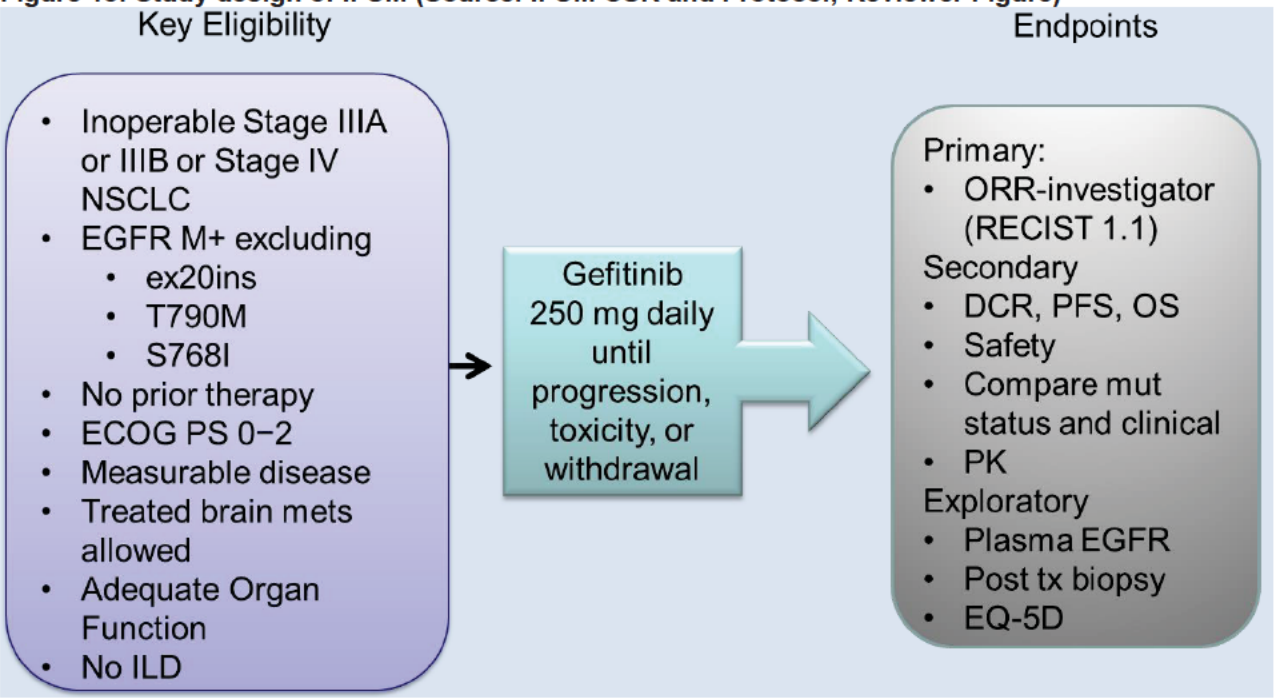
IFUM was an open-label, multicenter, single-arm study to characterize the efficacy and tolerability of gefitinib 250 mg as first-line treatment in Caucasian patients with EGFR M+ locally advanced or metastatic NSCLC. Patients were selected for gefitinib treatment on the basis of EGFR mutation status of their tumor sample at enrolment, regardless of clinical characteristics (eg, smoking history or histological subtype) using the Qiagen therascreen assay. EGFR mutation status was determined by mandatory formalin-fixed, paraffin-embedded tumor tissue samples and duplicate blood samples. Following screening procedures, all eligible patients were to receive gefitinib 250 mg once daily until objective disease progression, toxicity or, withdrawal of consent.

Baseline RECIST 1.1 assessment was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans no more than 28 days before, and as close as possible to, the start of study treatment (Visit 2). Baseline radiological assessments covered chest and abdomen (including adrenal glands). Any other areas of disease involvement were additionally investigated based on signs and symptoms of individual

patients. Radiological assessment using RECIST 1.1 was performed at screening and every 6 weeks after the start of study treatment until objective disease progression or until data cut-off for analysis, whichever occurred earlier. Following discontinuation of study treatment, further treatment and care was provided at the discretion of the investigator. If a patient discontinued study treatment due to objective disease progression, no further radiological tumor assessments were performed for the purpose of this study. If a patient discontinued study treatment for other reasons prior to the data cut-off analysis, the tumor assessments were continued according to the study plan until objective disease progression was documented or until the time of analysis, whichever occurred earlier.

Survival information was collected every 8 weeks until death, withdrawal of consent, loss to follow-up, or data cut-off date for analysis. Patients who had not progressed, who in the opinion of the investigator were continuing to receive benefit from treatment with gefitinib, and who could not access appropriate treatment outside of this clinical study were permitted to continue to receive open-label study treatment beyond the trial.

Figure 13: Study design of IFUM (Source: IFUM CSR and Protocol; Reviewer Figure)



Study Objectives:

Primary objective:

- To evaluate the ORR defined as confirmed complete response, (CR) or partial response (PR) of gefitinib using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, in Caucasian patients with EGFR mutation-positive (M+) NSCLC.

Secondary objectives:

- To evaluate disease control rate (DCR), progression free survival (PFS), and overall survival (OS) in Caucasian patients with EGFR M+ NSCLC.
- To evaluate the safety profile of gefitinib in Caucasian patients with EGFR M+ NSCLC.
- To define the correlation between clinical characteristics and baseline tumor EGFR mutation status in the screened NSCLC population.
- To characterize the pharmacokinetics (PK) of gefitinib taking into account demographic and clinical covariates in Caucasian patients with EGFR M+ NSCLC.

Exploratory objectives:

- To compare baseline tumor EGFR mutation status in all screened patients with evaluable results from baseline plasma.
- To compare plasma-derived cell-free (cf)DNA EGFR mutation status in duplicate baseline samples from the same patient to evaluate reliability of methodology in non-tumor samples.
- To compare plasma-derived cfDNA EGFR mutation status at baseline and at progression.
- To compare tumor sample EGFR mutation status at baseline and from an optional tumor sample taken at progression.
- To collect and store DNA derived from a blood sample for future exploratory research into genes that may influence response (eg, distribution, safety, tolerability, and efficacy) to gefitinib and/or susceptibility to NSCLC.
- To investigate patient health status index during the period of treatment with investigational therapy and 4 weeks after progression by assessment of the EuroQoL 5-dimension questionnaire (EQ-5D).

Eligibility Criteria:

Inclusion:

- Attainment of informed consent prior to any study specific procedures
- Caucasian female or male patients aged 18 years or over, eligible for standard first-line treatment for NSCLC

- Histologically confirmed NSCLC: adenocarcinoma, including bronchoalveolar carcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous carcinoma, or undifferentiated carcinoma. Cytological confirmation alone was not acceptable
- Locally advanced Stage IIIA/B (not suitable for therapy of curative intent) or Stage IV disease
- Measurable disease, defined as at least 1 lesion (not previously irradiated) that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which had to have short axis ≥15 mm) with spiral CT or MRI, and which were suitable for accurate repeated measurements
- World Health Organisation (WHO) performance status (PS) 0 to 2.
- For inclusion in the study at enrolment (Visit 1) and start of study treatment (Visit 2), patients had to be EGFR M+ NSCLC as determined by using a well-validated and robust methodology (also see exclusion criterion 5 below).

Exclusion:

1. Known severe hypersensitivity to gefitinib or any of the excipients of the product
2. Prior chemotherapy or other systemic anti-cancer treatment (including EGFR TKIs). Previous adjuvant chemotherapy was allowed, if completed more than 6 months prior to starting study treatment. Prior surgery or radiotherapy had to be completed more than 6 months before start of study treatment; palliative radiotherapy had to be completed at least 4 weeks before start of study treatment with no persistent radiation toxicity
3. Patients considered to require radiotherapy to the lung at the time of study entry or in the near future
4. Known or suspected brain metastases or spinal cord compression, unless treated with surgery and/or radiation and stable without steroid treatment for at least 4 weeks prior to the first dose of study medication
5. Presence of EGFR TK mutation reported to confer resistance to EGFR TKI: ie, Exon 20 point mutation (T790M or S768I EGFR) or Exon 20 insertion as determined by using a well-validated and robust methodology for mutations
6. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease
7. Pre-existing idiopathic pulmonary fibrosis evidenced by CT scan at baseline
8. Insufficient lung function as determined by either clinical examination or an arterial oxygen tension (PaO2) of <70 Torr
9. Any unresolved chronic toxicity greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 2 from previous anticancer therapy
10. Concomitant use of known cytochrome P450, subfamily IIIA, polypeptide 4 (CYP3A4) inducers such as phenytoin, carbamazepine, rifampicin, barbiturates, or St John's wort
11. Pregnancy or breast-feeding

12. As judged by the investigator, any evidence of severe or uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)
13. Evidence of any other significant clinical disorder or laboratory finding that made it undesirable for the patient to participate in the study
14. Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or cervical cancer in situ
15. Life expectancy of less than 12 weeks
16. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment
17. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site)
18. Previous enrolment or treatment in the present study.

Determination of EGFR mutation status:
The designated central laboratory, (b) (4), evaluated the EGFR mutation status of individual tumor samples for each of the mutations included in the Qiagen therascreen EGFR RGQ PCR kit. Based on the mutation results and eligibility criteria, the following overall EGFR mutation status was assigned to each of the individual tumour samples:

- Tumor samples that were positive for ≥1 activating sensitizing EGFR mutations and where no mutations defined as making the patient ineligible for the study were detected were assigned the status **EGFR M+**.
- Tumor samples that were positive for mutations defined as making the patient ineligible for the study were assigned the status **EGFR M+I**.
- Tumor samples for which no mutations were detected were assigned the status **M-**.
- Tumor samples for which no mutation results were available were assigned overall mutation **status unknown**.

Criteria for Patient Discontinuation from Study or Therapy:

Patients were discontinued from investigational product in the following situations:

- Patient's decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to study protocol
- Objective disease progression according to RECIST 1.1.

Treatment Agents:

Eligible patients were treated with open-label gefitinib 250 mg oral tablets once daily, administered continuously from Visit 2 until objective disease progression was documented or any other criterion for discontinuation (eg, toxicity, withdrawal of consent) was met. Gefitinib tablets were taken at approximately the same time each day.

Prior surgery or radiotherapy was allowed, if completed >6 months before the start of study treatment. Palliative radiotherapy was acceptable, if completed ≥4 weeks before the start of study treatment with no persistent radiation toxicity. Previous adjuvant chemotherapy was allowed, if completed more than 6 months prior to starting the study treatment. Prior chemotherapy or other systemic anti-cancer treatment (including EGFR TKIs) was not allowed.

No additional systemic anti-cancer treatment could be used except for bisphosphonates for treatment of bone pain or hypercalcemia. Palliative radiotherapy for painful bone metastases or to other non-pulmonary metastatic sites was allowed. However, if palliative radiotherapy to the lung was required, gefitinib had to be discontinued and the patient had to be followed for radiation toxicity. Any lesion subjected to radiation therapy was no longer considered evaluable for response but continued to be followed for progression.

Phenytoin, carbamazepine, rifampicin, barbiturates, and St. John's wort were not allowed (these drugs induce CYP3A4 and could decrease the levels of gefitinib). Patients taking potent CYP3A4 inhibitors were monitored closely for adverse reactions. Itraconazole, for example, resulted in an 80% increase in gefitinib mean AUC in healthy volunteers. Such an increase in exposure could be clinically relevant because adverse experiences are related to dose and exposure. Co-administration was not precluded in this study because doses higher than gefitinib 250 mg have been investigated and considered tolerable. Patients taking drugs that cause significant sustained elevations in gastric pH >5 was not allowed. Patients taking warfarin were monitored regularly for changes in their prothrombin time or international normalized ratio.

Dose Modifications and Management of Toxicities:

Dose interruptions were to be used as the first approach to managing toxicity. Repeat dose interruptions were allowed as required, for a maximum of 14 days on each occasion. Dose reductions were not permitted in this study. For any other CTCAE grade 3 or 4 toxicity or any clinically significant lower grade toxicity, treatment with gefitinib should be interrupted until the patient recovers completely or the toxicity reverts to CTCAE grade 1 or to the baseline grade. In all cases where the patient has been

withdrawn due to unusual or unusually severe toxicity considered related to gefitinib, the investigator must contact the AstraZeneca study physician.

Specific guidelines for certain toxicities were included in the protocol:

1. Management of skin toxicity
    - Patients with poorly tolerated skin toxicity may be managed by providing a brief interruption of gefitinib; the daily dose of gefitinib should then be reinstated.
    - However, the rash may improve without the need for interrupting gefitinib therapy.
    - Investigators have had varying degrees of success with a variety of agents used to manage skin rashes including mild to moderate strength steroid creams, either topical or systemic antihistamines and occasionally retinoid creams. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation.
2. Management of gastrointestinal toxicity
    - Patients should be advised to seek medical advice promptly in the event of developing severe or persistent diarrhea, nausea, vomiting or anorexia
3. Liver transaminases
    - Liver function test abnormalities have been observed, uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure which in some cases led to fatal outcomes and therefore, periodic liver function testing is recommended.
    - Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.
4. Ophthalmology
    - Patients should be advised to seek medical advice promptly in the event of developing any eye symptoms.
5. Management of Interstitial Lung Disease (ILD)
    - Interstitial lung disease (ILD), including interstitial pneumonitis, is a common complication of lung diseases including advanced lung cancer, regardless of treatment. It has also been widely observed in clinical studies in which chemotherapy (incidence generally ranges from 3 to 6%) and/or radiotherapy (incidence generally ranges from 10 to 15%) has been used for the treatment of advanced lung cancer.
    - If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient promptly investigated for ILD. If ILD is

confirmed, gefitinib should be discontinued and the patient treated appropriately.

Study Assessments:

An independent Central review of all scans was planned for the assessment of tumors using RECIST 1.1. All imaging assessments including unscheduled visit scans were to be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organization (CRO) for central analysis. Results of the independent review was not to be communicated to investigators, and the management of patients was to be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator. The primary versions of the RECIST-derived outcome variables were to be based on the tumor assessments recorded on the eCRF (clinical database; as collected via the investigator). Versions derived from the Central Review were to be considered secondary and confirmatory and were derived from the independent review visit responses and the dates of the scan assessment visits.

All serious adverse events (SAEs) were to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs were to be recorded in the eCRF.

Statistical Plan:

The study planned to recruit 100 eligible EGFR M+ patients to be treated with gefitinib. It was expected that screening approximately 1250 Caucasian NSCLC patients would be sufficient to obtain 100 eligible patients with EGFR M+ NSCLC. Screening and recruitment were to cease when 100 patients had started study treatment. One-hundred EGFR M+ patients would allow precise estimation of the ORR, with the lower limit of the 95% CI lying within 10% of the observed ORR.

The table below describes the study populations used to analyze the various endpoints.

Table 5: Description of study populations (Source: IFUM CSR and Protocol; Reviewer Table)

Analysis Population	Description	Outcome
All Screened Patients	All patients proposed for the study, who were assessed for EGFR mutation status	• Correlation between clinical characteristics and EGFR mutation status • Comparison of EGFR mutation status between tumor DNA and plasma-derived cfDNAb • Comparison of cfDNA EGFR mutation status in duplicate baseline plasma samples
Full analysis set (FAS) (Primary study population)	A subset of all screened patients, who were found to be EGFR M+ and who had taken at least 1 dose of study treatment.	• ORR • DCR, PFS and OS • Comparison of EGFR mutation status in plasma and tumor samples at baseline and at progression.
Evaluable for safety (EFS)	All patients who received at least 1 dose of study medication.	• Safety Data
PK analysis set	Patients in the FAS, having at least 1 measurable PK concentration, supported by the relevant date and time for the particular sample and dates and times of the doses administered 2 days prior to sampling.	• Gefitinib plasma concentrations

ORR was calculated as the percentage of EGFR M+ patients who had taken at least 1 dose of study treatment and had a confirmed CR or PR by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits (as defined by RECIST 1.1). The primary derivation of ORR (investigator review) was calculated from the data collected on objective tumor assessment (ie, derived based on the individual target lesions, overall assessment of non-target lesions, and new lesion data recorded by the investigator in the clinical database). A supportive ORR derivation (central review) was calculated from the central review of scans by an independent reviewer. The analysis of ORR used the primary study population. ORR was only summarized. The 95% CIs for the ORR were derived using Wilson score intervals.

Changes to the Protocol:

Table 6: Important Study IFUM Protocol Amendments (Source: IFUM CSR and Protocol; Reviewer Table)

Amendment#	Version Date	Summary of Changes
2	13 June 2012	• Patients, who had not progressed and derived benefit from the treatment, but who could not access appropriate treatment outside of this study, were allowed to continue the study treatment beyond the data cut-off. • The requested study procedures after the data cut-off were clarified • Study specific discontinuation criteria for patients receiving study treatment after data cut-off were added.
1	27 January 2011	• The ORR, PFS, DCR, and OS analysis was also to be conducted for positive EGFR mutations types.

Table 7: Key changes to the planned analysis (Source: IFUM CSR and Protocol; Reviewer Table)

Justification	Details of the changes
Analysis of subset of the EGFR M- patients (n =100) would provide data equally informative to that to be obtained from all EGFR M-patients (n=1000).	• Duplicate plasma samples were collected to evaluate the plasma EGFR mutation status from all screened patients. The first replicate was analyzed for all screened patients. The second replicate was planned to be analyzed for all EGFR mutation-positive patients (EGFR M+ and EGFR M+I, n=114) and for approximately the same number of EGFR M- patients (n=111) who were selected randomly from those who had 2 plasma samples
To provide consistency between analysis of efficacy objectives (primary and secondary) and biomarker objectives	• EGFR M+I patients were excluded from the analysis of the secondary objective relating to biomarkers

STUDY IPASS:

The purpose of this study was to compare gefitinib at a dose of 250 mg daily with carboplatin (AUC 5.0 or 6.0) / paclitaxel (200 mg/m^2 every 3 weeks) for first-line treatment of non-small cell lung cancer (NSCLC) in clinically selected patients. The study set out to determine whether gefitinib 250 mg was non-inferior to carboplatin / paclitaxel in terms of progression free survival (PFS). Patients in Asia with Stage IIIB or IV adenocarcinoma of the lung, who were never smokers or light ex-smokers, were selected. This study supports the pivotal study for this NDA submission and is titled:

An Open Label, Randomized, Parallel Group, Multicenter, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib Versus Carboplatin / Paclitaxel Doublet Chemotherapy as First-Line Treatment in Selected Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) in Asia (IPASS)

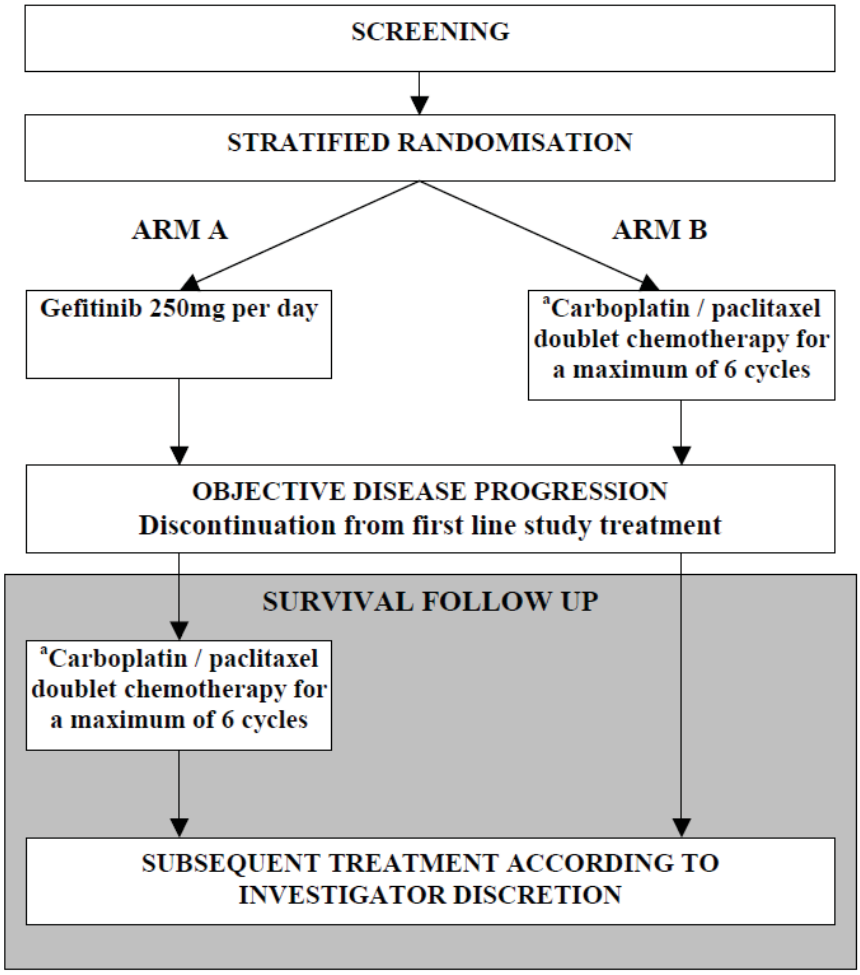
Design and treatment plan:

This was an open-label, randomized, parallel-group, Phase III study comparing gefitinib to carboplatin / paclitaxel doublet chemotherapy in patients with stage IIIB or stage IV adenocarcinoma lung in the first-line setting. A total of 1212 patients (606 per treatment group) were expected to be randomized during a 20-month recruitment. Patients were recruited by investigational centers throughout Asia (approximately 75 centers in total). It was estimated that approximately 200 patients were to be recruited in Japan, approximately 300 patients in China and approximately 712 patients from elsewhere in Asia. This study recruited male or female never smokers or light ex-smokers (defined as having ceased smoking at least 15 years before Day 1 of study treatment and having smoked 10 pack-years or fewer) aged 18 years or older with a World Health Organization (WHO) Performance Status (PS) 0-2, and measurable disease according to RECIST criteria. Patients must have histologically or cytologically confirmed advanced (Stage IIIB, not amenable to local therapy, or Stage IV) adenocarcinoma lung, and not have received any previous chemotherapy excluding post operative adjuvant monotherapy.

Eligible patients were randomized in a 1:1 ratio to receive either Arm A, gefitinib 250 mg daily (oral tablet) followed by carboplatin / paclitaxel doublet chemotherapy or Arm B, carboplatin / paclitaxel doublet chemotherapy. In arm A, gefitinib was administered daily until objective progressive disease (PD) or other criteria for discontinuation are met. In arm B, first line carboplatin / paclitaxel doublet chemotherapy will be administered for a maximum of 6 cycles. Chemotherapy will be discontinued if objective progressive disease (PD) or other criteria for discontinuation is met. Patients who complete all chemotherapy cycles without documented objective PD should continue to attend clinic visits and undergo tumor assessments until objective PD was documented.

Tumor assessment using RECIST was performed at baseline then every 42 days (6 weeks) ± 7 days (1 week) from randomization. Patients were evaluated until progression, and will then followed for survival until death, loss to follow-up, withdrawal of informed consent or final data cut-off for analysis. Following data cut-off for the primary endpoint (when 944 progression events have occurred), data collection was limited to survival status and subsequent anti-cancer treatments collected every 56 days (8 weeks). SAEs will be collected for those patients continuing on study treatment or second line treatment provided by the Sponsor. Following data cut-off for the survival endpoint (when 944 deaths occurred), data collection was limited to SAEs for those patients continuing on study treatment or second line treatment provided by the Sponsor.

Figure 14: IPASS trial design(Source: IPASS CSR and Protocol; Applicant Figure)



Study Objectives:

Primary objective:

- To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of PFS in selected NSCLC patients (non-inferiority).

Secondary objectives: To compare the randomized treatment arms in terms of

- OS
- ORR according to RECIST
- the safety and tolerability profile of gefitinib at a 250 mg daily dose
- quality of life (QOL) as measured by the total score and Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Lung Cancer (FACT-L) questionnaire
- symptom improvement as measured by the Lung Cancer Subscale (LCS) of the FACT-L questionnaire

The exploratory objectives of the study were to compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of

- health care resource use in a subset of patients (at centers in Taiwan and Thailand).
- to investigate baseline biomarker data in consenting patients to ascertain if there are any biomarkers that differentiate for a relative treatment effect when comparing the randomized treatment arms.

Eligibility Criteria:

Inclusion:

1. Provision of informed consent
2. Male or female aged 18 years and over
3. Histologically or cytologically confirmed non-small cell lung carcinoma with adenocarcinoma histology (including bronchoalveolar). Note: adeno-squamous histology is not allowed. Sputum cytology alone is not acceptable. Cytological specimens obtained by brushing, washing, or needle aspiration of a defined lesion are acceptable.
4. Locally advanced Stage IIIB not amenable to local therapy (e.g. pleural effusion) or Stage IV (metastatic) disease.
5. Never smokers or light ex-smokers (defined as having ceased smoking at least 15 years before Day 1 of study treatment and having smoked 10 pack-years or fewer)
6. No prior chemotherapy, biological (including targeted therapies such as EGFR and vascular epidermal growth factor (VEGF) inhibitors) or immunological therapy. Previous adjuvant chemotherapy is permitted if treatment was not platinum-based and was completed more than 6 months before Day 1 of study treatment. Prior surgery or radical radiotherapy must be completed more than 6

months before Day 1. Palliative radiotherapy to a metastatic site is permitted, but palliative wide field radiotherapy to the lung must be completed at least 4 weeks before day 1 with no persistence of any radiotherapy-related toxicity.
7. Measurable disease according to RECIST criteria with at least one measurable lesion not previously irradiated (see Appendix C).
8. World Health Organization (WHO) performance status (PS) of 0 to 2
9. Patients must be willing to complete the FACT-L questionnaire

Exclusion criteria:
1. Known severe hypersensitivity to gefitinib or any of the excipients of this product
2. Known severe hypersensitivity to carboplatin, paclitaxel or any of the excipients of these products
3. Known severe hypersensitivity to pre-medications required for treatment with carboplatin / paclitaxel doublet chemotherapy
4. Newly diagnosed Central Nervous System (CNS) metastases that have not yet been definitively treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression may be considered if they are clinically stable and have been discontinued from steroid therapy for at least 4 weeks prior to first dose of study medication.
5. History or presence of any other malignancy with the exception of basal cell carcinoma or cervical cancer in situ
6. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease
7. Pre-existing idiopathic pulmonary fibrosis evidence by CT scan at baseline
8. Any unresolved chronic toxicity greater than CTCAE grade 2 from previous anticancer therapy
9. Absolute neutrophil counts (ANC) less than 2.0 x 10^9/L (2,000/mm^3), platelets less than 100 x 10^9/L (100,000/mm^3) or haemoglobin less than 10 g/dl
10. Serum bilirubin greater than 1.5 times the upper limit of reference range (ULRR).
11. Serum creatinine greater than 1.5 times the ULRR or creatinine clearance less than or equal to 60 ml/min
12. As judged by the investigator, any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic or renal disease).
13. Evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study.
14. Alanine amino transferase (ALT) or aspartate amino transferase (AST) greater than 2.5 times the ULRR if no demonstrable liver metastases or greater than 5 times the ULRR in the presence of liver metastases.
15. Pregnancy or breast-feeding
16. Insufficient lung function as determined by either clinical examination or an arterial oxygen tension (PaO2) of < 70 Torr

17. Unable to tolerate carboplatin / paclitaxel doublet chemotherapy, as judged by the investigator.
18. Life expectancy of less than 12 weeks
19. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort
20. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment.
21. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)
22. Previous enrolment or randomization of treatment in the present study

Criteria for Patient Discontinuation from Study or Therapy:

Criteria for discontinuation from study treatment:

- Patient has received maximum number of protocolled carboplatin / paclitaxel cycles.
- Dose delay or interruption for > 14 days
- Symptomatic deterioration as judged by the investigator
- Voluntary discontinuation by the patient who is at any time free to withdraw from study treatment or assessments, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AZ
- Severe non-compliance to protocol as judged by the investigator and/or AZ
- Objective progression of disease

Criteria for termination from study:

- Voluntary withdrawal by the patient who is at any time free to terminate his/her participation in the study, without prejudice to further treatment
- Patient lost to follow-up
- Death

In addition to the above, patients will terminated from study during the screening phase for:

- Incorrect enrolment (ie, the patient does not meet the required inclusion/exclusion criteria) of the study, and may be terminated during the screening phase for safety reasons as judged by the investigator and/or AZ.

Treatment Agents:

The gefitinib dose level for this study is 250 mg daily. One tablet of gefitinib was taken at each administration, about the same time every day, with or without food. If the patient forgot to take a dose, they were to take the last missed dose as soon as they remember, as long as it was at least 12 hours before the next dose was due. Study treatment was dispensed to patients on Day 1 and every 84 days (12 weeks) thereafter

during the treatment period until the patient had documented objective PD or other criteria for discontinuation are met as described in section 3.3.5. Patients randomized to receive gefitinib were instructed to begin their study treatment within 72 hours of randomization.

Patients received paclitaxel 200mg/m^2 intravenous (iv) over 3 hours on Day 1, immediately followed by carboplatin AUC 5.0 or 6.0 IV over 15-30 minutes, repeated in cycles of 3 weeks for a total of 6 cycles.

Dose Modifications and Management of Toxicities:

Gefitinib: Dose interruptions were to be used as the first approach to managing toxicity. Repeat dose interruptions were allowed as required, for a maximum of 14 days on each occasion. Dose reductions were not permitted in this study.

Carboplatin/Paclitaxel: The protocol included guidelines, however local practice, prescribing information and clinical judgment was to followed for the management of toxicities.

Study Assessments were performed per the protocol

Statistical Plan:

Statistical analysis was to take place in two stages. The primary analysis was to take place after 944 progression events have occurred and to include all primary and secondary outcome variable data available at the time of data cut-off, apart from overall survival. Patients were to then continue to be followed up for overall survival and a second analysis will take place after 944 deaths have occurred. This was to include the overall survival outcome variable only.

Table 8: Description of outcome variables for IPASS (Source: IPASS CSR and Protocol; Reviewer Table)

Objective	Outcome Variable
Primary Objective	
To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first line treatment in terms of progression free survival.	**Progression-free survival (PFS)**
Secondary Objectives	
To compare the randomized treatment arms in terms of overall survival.	**Overall objective tumor response (complete response (CR) and partial response (PR)) as per the Response Evaluation in Solid Tumors (RECIST) criteria**
To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first line treatment in terms of objective response rate	
To compare the safety and tolerability profile of gefitinib at a 250 mg daily dose given as first line treatment relative to that of carboplatin / paclitaxel doublet chemotherapy given as first line treatment	Nature, incidence and severity of adverse events (AEs) and serious adverse events(SAEs) Incidence of and reasons for study drug dose interruptions and withdrawals Laboratory assessments and physical examinations
To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first line treatment in terms of quality of life	Quality of life as measured by the total score and Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy –Lung Cancer (FACT-L) questionnaire
To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first line treatment in terms of symptom improvement	Symptom improvement as measured by the Lung Cancer Subscale (LCS) of the FACT-L questionnaire
Exploratory Objectives	Health care resource use including: inpatient hospital visits, outpatient visits, emergency room visits, major medical procedures.
To compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first line treatment in terms of health care resource use in a subset of patients	
To investigate baseline biomarker data to ascertain if there are any biomarkers that differentiate for a relative treatment effect when comparing randomized treatment arms.	Biomarkers as below: - Expression, activation and dimerization of EGFR and other HER family receptors and associated pathways including downstream signaling pathways - Somatic (non-inheritable) mutation and

	copy number analyses of genes of the ErbB family, their signaling pathways and associated pathways which are thought to be influenced by gefitinib in tumor cells - RNA expression profile (including candidate marker genes).

The primary statistical analysis was to compare the PFS between first line gefitinib and first line carboplatin/paclitaxel using a proportional hazards model adjusted for performance status (0-1 vs 2), smoking history (never vs light ex-smoker), and gender. The null hypothesis of survival inferiority was to be rejected and non-inferiority will be concluded if the upper 95% confidence limit of the hazard ratio was below 1.2.

According to the Applicant, a non-inferiority design was chosen because it is of interest to show if gefitinib is at least as effective as chemotherapy given that the side effect profile of gefitinib is modest and non-life threatening in comparison with the severe burden of toxicity associated with standard chemotherapy. The non-inferiority limit chosen for PFS was a hazard ratio of 1.2, which translates to up to 1 month shortfall on gefitinib if the PFS on carboplatin/paclitaxel is 6 months. This was felt to be the maximum shortfall that would be acceptable taking into account the potential advantages of a generally well tolerated oral agent compared to standard intravenous chemotherapy. For overall survival, given the relatively short life expectancy of this population of patients, a shortfall greater than 7 weeks was felt to be clinically significant given that chemotherapy is offered despite only relatively modest improvements in overall survival compared to BSC

Changes to the Protocol:

Table 9: Key changes to the IPASS protocol (Source: IPASS CSR and Protocol; Reviewer Table)

Details of the changes
The definition of never smokers was added as those who have smoked less than 100 cigarettes per life time.
Non-platinum based adjuvant chemotherapy was an exception to the exclusion criteria.
Allowance of the use of bisphosphonates and G-CSF
No adjustment of significance level for the final analysis as there was no opportunity at the interim to accept non-inferiority for PFS.
Allowance of cytology sample collection
Provision to allow provision of regular data updates to the IDMC.
Amendment of the optional biomarker research sections 5.1, 8.3 and 8.4. An additional patient informed consent form was added.
The amendment contained some clarifications relating to the data cut off for the survival endpoint (when 944 death events have occurred) and the closure of the study.
An amendment clarifying the collection procedure for adverse events in patients ongoing at the progression free survival primary analysis
The study team plan for collection of all tumor assessment scans and storage centrally at a CRO in order to satisfy any potential regulatory requests for independent review.

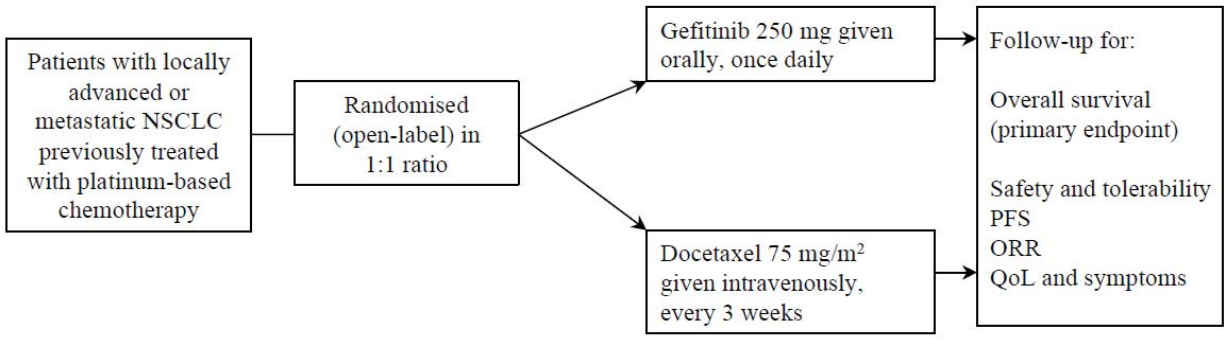
INTEREST:

A Randomized, Open-label, Parallel-group, International, Multicenter, Phase III Study of Oral ZD1839 (IRESSA) versus Intravenous Docetaxel (TAXOTERE) in Patients with Locally Advanced or Metastatic Recurrent Non-small Cell Lung Cancer who have Previously Received Platinum-based Chemotherapy

Design and treatment plan:

This is a randomized, open-label, parallel-group, phase III, multicenter international study. The total number of patients expected to be randomized to receive study treatment was approximately 1440. Patients were recruited by investigational sites throughout the world with expertise in treating patients with NSCLC. Patients were randomized to either gefitinib 250 mg/day, orally or docetaxel 75 mg/m^2 every 3 weeks, intravenously over 1 hour. The target population was patients who had received prior platinum-based chemotherapy, had progressive or recurrent disease and were now considered candidates for further chemotherapy with docetaxel. Refractory to platinum and/or paclitaxel was defined as progression on, or within, 3 months of completing platinum or paclitaxel therapy. At study entry, patients were randomized on a 1:1 basis using dynamic balancing (Pocock and Simon 1975) with respect to histology (adenocarcinoma vs other), performance status (0 or 1 vs 2), prior platinum therapy (refractory vs received), prior paclitaxel therapy (refractory vs received vs none), prior regimens (1 vs 2), smoking history (ever vs never), and center. Patients continued to receive treatment with either gefitinib or docetaxel until disease progression, unacceptable toxicity, or the occurrence of any of the other protocol specific criteria.

Figure 15: INTEREST study design (Source: INTEREST CSR and Protocol; Applicant Figure)



Study Objectives:

Primary Objectives: To compare overall survival between gefitinib and docetaxel, using the following pre-defined co-primary analyses:

- An assessment of non-inferiority in the overall per protocol (PP) population, and if accepted, an assessment of superiority in the overall intention to treat (ITT) population
- An assessment of superiority in the ITT EGFR FISH+ population

Secondary objectives:
- To compare PFS between gefitinib and docetaxel
- To compare progression-free rates at 4 months and 6 months between gefitinib and docetaxel
- To compare the overall ORR between gefitinib and docetaxel
- To compare PRF and QOL between gefitinib and docetaxel
- To compare safety and tolerability of gefitinib and docetaxel

Exploratory objectives
- To correlate tumor EGFR protein expression and the status of other related biomarkers, including mutation status for the EGFR gene and for genes of associated pathways, with efficacy of gefitinib
- To correlate baseline profiles and modulation of biomarkers in serum, plasma and urine (including plasma and urine proteomics, serum cytokines [US sites only] and metabalomics) evaluated at baseline and during therapy with measures of patient outcome (such as response rate or QOL measures)
- To evaluate pulmonary symptom changes (in symptomatic US and Latin American patient population only) between gefitinib and docetaxel
- To investigate the potential correlation between spirometry and pulmonary symptoms
- To evaluate patient-reported perceptions of treatment side effects between gefitinib and docetaxel
- To evaluate changes in pain and fatigue (in symptomatic US and Latin American patient population only) between gefitinib and docetaxel
- To evaluate a patient-reported global assessment of change in pulmonary symptoms between gefitinib and docetaxel, which will potentially provide an anchoring of the pulmonary symptoms endpoint to patient-perceived clinical benefit (in symptomatic US and Latin American patient population only)
- To evaluate the health care resource use by patients between gefitinib and docetaxel

Eligibility Criteria:

Inclusion criteria:
1. provision of written informed consent
2. aged 18 years or older

3. histological or cytological confirmation of NSCLC (from initial diagnosis of NSCLC or subsequent biopsy). (Note: sputum cytology alone was not acceptable. Cytological specimens obtained by brushing, washing or needle aspiration of a defined lesion were acceptable).
4. locally advanced or metastatic NSCLC that was not amenable to curative surgery or radiotherapy
5. one or two prior chemotherapy regimens, at least one of which must have been platinum-based
6. measurable (unidimensional) disease by RECIST criteria in a lesion not previously irradiated, or non-measurable disease (ie, the patient was to have at least one lesion at baseline - either target lesion or non-target lesion)
7. World Health Organization (WHO) performance status (PS) of 0, 1, or 2
8. absolute neutrophil count (ANC) >1.5x10^9/L and platelets >100x10^9/L
9. adequate hepatic function, defined as BOTH a bilirubin less than or equal to the upper limit of the reference range (ULRR) AND an 'eligible' combination of transaminases (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) and alkaline phosphatase (ALP).

Figure 16: Eligibility criteria regarding liver enzymes for INTEREST (Source: INTEREST CSR and Protocol; Reviewer Table)

Alk Phos	AST or ALT			
	≤ULRR	>1x but ≤1.5x	>1.5x but ≤5x	>5x ULRR
≤ULRR	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULRR	Ineligible	Ineligible	Ineligible	Ineligible

10. recovery from all acute toxicities of prior therapies
11. life expectancy of at least 8 weeks

Exclusion criteria:

1. prior gefitinib therapy or prior therapy with an experimental agent whose primary mechanism of action was inhibition of EGFR or its associated tyrosine kinase
2. prior docetaxel treatment for NSCLC
3. newly diagnosed CNS metastases that had not yet been treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression could be considered if they had evidence of clinically stable disease (no steroid therapy or steroid dose being tapered) for at least 28 days.
4. less than 14 days since the completion of prior radiotherapy or persistence of any radiotherapy related toxicity
5. less than 21 days since prior chemotherapy, immunotherapy, or biological systemic anticancer therapy

6. any unresolved chronic toxicity from previous anticancer therapy that, in the opinion of the investigator, made it inappropriate for the patient to be enrolled in the study
7. known, severe hypersensitivity to gefitinib or any of the excipients of this product
8. known hypersensitivity to docetaxel, polysorbate 80 or other drugs formulated with polysorbate 80, or any of the excipients of docetaxel
9. other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or cervical cancer in situ
10. inability to swallow tablets
11. any evidence of clinically active interstitial lung disease (ILD) (patients with chronic, stable, radiographic changes who were asymptomatic or patients with uncomplicated progressive lymphangitic carcinomatosis need not be excluded)
12. in the opinion of the investigator, any evidence of severe or uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)
13. evidence of any other significant clinical disorder or laboratory finding that made it undesirable for the patient to participate in the study
14. incomplete healing of the surgical incision from prior major surgery (small biopsy wounds would not prohibit the patient from study entry)
15. signs of neurological symptoms consistent with new onset spinal cord compression
16. patients with pre-existing peripheral neuropathy ≥Grade 2 (National Cancer Institute common toxicity criteria [NCI CTC])
17. pregnancy or breast-feeding (women of childbearing potential)
18. concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort
19. treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment

Criteria for Patient Discontinuation from Study or Therapy:

Patients could be discontinued from study treatment and assessments at any time, at the discretion of the investigator(s). Patients were to be followed for survival information after discontinuation for any reason (except withdrawal of consent by the patient or patient lost to follow-up). Similarly, progression information was to continue to be collected via RECIST if the patient had not yet progressed at the time of discontinuation. Specific reasons for discontinuing a patient from study treatment or assessments were:

1. safety reasons (adverse events) as judged by the investigator and/or AZ
2. severe non-compliance with the protocol as judged by the investigator and/or AZ (unless the patient was benefiting from protocol therapy)
3. radiological, objective progression of disease. If an investigator believed that a patient had convincing evidence of 'clinical progression' (eg, worsening PS that was clearly cancer related) but, despite adequate imaging, it was not possible to

document objective radiological progression, the patient should have been discussed with the AZ physician and a decision on discontinuation of study therapy made on a case-by-case basis. Additionally, radiological progression alone need not necessarily require the discontinuation of study therapy if, following discussion with the AZ physician, the patient was still deemed to be deriving clinical benefit. In such situations, the patient was able to continue to receive study drug but the correct date of objective disease progression had to be documented.

4. Death
5. patient lost to follow-up

Treatment Agents:

- gefitinib 250 mg tablets once daily for each of the 21-day cycles
  or
- docetaxel 20 mg or 80 mg injection 75 mg/m^2, administered intravenously over 1 hour, every 3 weeks (1 cycle = 21 days).

Statistical Plan:

Statistical analyses were carried out by the Biostatistics Group at AstraZeneca (Alderley Park, UK). Statistical tests were 2-sided and were generally tested at the 5% level of significance. However, following full evaluation of the ISEL study results, including the biomarker data, the protocol was amended to incorporate a co-primary analysis of overall survival for patients with high EGFR gene copy number. Coprimary analyses of overall survival therefore compared gefitinib 250 mg to docetaxel 75 mg/m^2 in (1) all patients and (2) patients with high EGFR gene copy number. To ensure that the overall type-I error rate was not inflated by having these 2 co-primary analyses, a modified Hochberg procedure was employed which split the overall 5% alpha into 4% and 1% rather than the usual 2.5% equal split in the standard Hochberg procedure.

Changes to the Protocol:

The original protocol was dated 17 October 2003 and there were 4 amendments.

Table 10: Key changes to the protocol (Source: INTEREST CSR and Protocol; Reviewer Table)

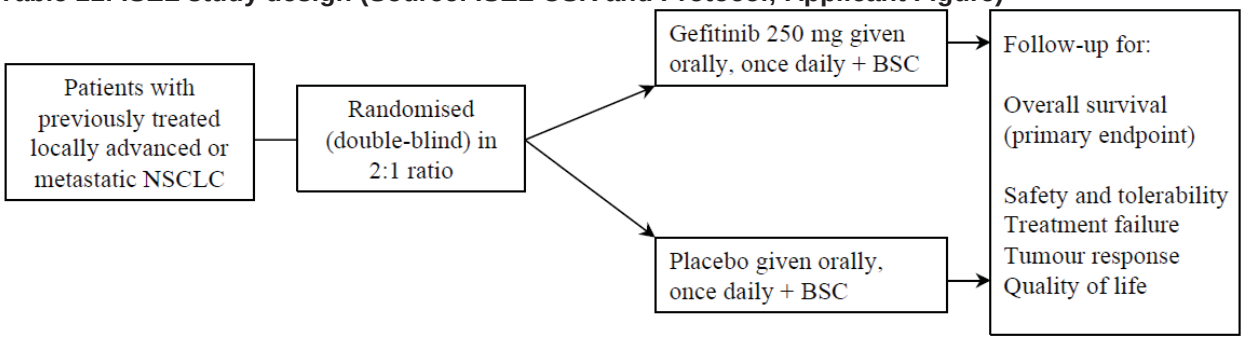
Amendment	Details	Reasons
1 **14 September 2004**	Biomarker evaluations amended to include the measurement of the recently discovered somatic EGFR mutations in the tumors of patients who responded to gefitinib therapy. Appendix to clarify guidance on acceptable platinum therapy added.	Publications indicated somatic EGFR mutations may predict for responsiveness to gefitinib. To provide further clarification and explanation.
2 **14 March 2006**	The accrual period was extended to 24 months. ISEL and SIGN results were incorporated.	Due to lower than expected recruitment. New information available from two studies including the Phase III ISEL study.
3 **1 August 2006**	Addition of co-primary analyses in the subgroup of EGFR FISH+ patients.	Following results from ISEL and other studies suggesting EGFR FISH+ patients most likely to derive benefit from gefitinib.
4 **29 January 2007**	Clarification of data collection procedure following data cut off and provision of study medication after the survival results are known.	Original protocol unclear.

ISEL: A Double-blind, Placebo-controlled, Parallel-group, Multicenter, Randomized, Phase III Survival Study Comparing ZD1839 (IRESSA) (250 mg Tablet) plus Best Supportive Care versus Placebo plus Best Supportive Care in Patients With Advanced NSCLC who Have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen

Design and treatment plan:

This was a randomized, double-blind, placebo-controlled, parallel-group, international, multicenter study, designed to assess whether the addition of gefitinib (250 mg daily) to BSC in patients with previously treated locally advanced or metastatic NSCLC conferred an overall survival advantage over placebo plus BSC. On the basis of increased response rates and their durability observed in an uncontrolled Phase II setting, this study was designed with the primary objective that gefitinib would confer a statistically significant survival advantage among patients with adenocarcinoma histology; if a survival advantage was detected in this population, a subsequent survival analysis was to be carried out in the overall population. Approximately 866 patients with adenocarcinoma, accrued over 12 months, were to be recruited into the study, and it was estimated that this would lead to approximately 1299 patients being recruited in total.

Table 11: ISEL study design (Source: ISEL CSR and Protocol; Applicant Figure)



Study Objectives:

Primary objectives:
The primary objective was to compare overall survival for gefitinib plus BSC versus placebo plus BSC.

Secondary objectives:
The secondary objectives were to compare gefitinib plus BSC versus placebo plus BSC in terms of:

- time to treatment failure

- investigator assessed overall objective tumor response (complete response [CR] + partial response [PR])
- quality of life changes
- tolerability

Exploratory objective:
To investigate the correlation of EGFR and other related biomarker status with efficacy in those patients where such tumor material was available.

Eligibility Criteria:

Inclusion criteria:

1. provision of written informed consent
2. age 18 years or older
3. histologically or cytologically confirmed non-small cell bronchogenic carcinoma:
    a. adenocarcinoma (including bronchoalveolar),
    b. squamous cell carcinoma,
    c. large cell carcinoma or mixed (adenocarcinoma and squamous) or
    d. undifferentiated carcinoma
4. locally advanced or metastatic NSCLC, which was not amenable to curative surgery or radiotherapy
5. not considered to have required palliative radiotherapy at the time of study entry or in the near future not considered to have been suitable by the investigator or patient had refused further treatment with cytotoxic chemotherapy (second-line patients)
6. previously received at least 1 but no more than 2 prior chemotherapy regimens (prior surgery and/or localized irradiation were allowed)
7. for patients aged <70 years at initial diagnosis, at least one prior chemotherapy regimen must have included a platinum agent, but elderly patients (≥70 years of age at initial diagnosis) need not have received platinum therapy and could have received 1 or 2 prior non-platinum or single-agent regimens
8. refractory (defined as recurrent or progressive disease [clinical or radiological] while receiving or within 90 days of last dose of chemotherapy) or intolerant to their most recent prior chemotherapy regimen. Patients were considered intolerant to their most recent chemotherapy regimen if they had experienced one or more of the following:

    a. anaphylaxis to taxane
    b. CTC grade 2 or greater neuropathy
    c. prior history of CTC grade 4 neutropenia (associated with severe or life threatening infection or occurring twice or more with prior chemotherapy)
    d. prior history of CTC grade 4 thrombocytopenia with associated significant haemorrhage

e. inability to tolerate large volume intravenous fluids due to congestive heart
f. failure
g. measurable (uni-dimensional) disease by RECIST criteria or non-measurable disease
h. WHO PS 0, 1, or 2. Patients of PS 3 were eligible unless the investigator believed the poor PS was predominantly due to co-existing morbidity (eg, previous cerebrovascular accident, debilitating rheumatoid arthritis, or severe cardiac impairment)
i. life expectancy of at least 8 weeks.

Exclusion criteria:

1. small cell lung cancer or mixed small and NSCLC
2. newly diagnosed CNS metastases that had not been treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression could be considered if they had evidence of clinically stable disease (no steroid therapy or steroid dose being tapered) for at least 2 weeks
3. less than 1 week since the completion of their prior radiotherapy or persistence of any radiotherapy-related toxicity
4. more than 2 prior chemotherapy regimens for treatment of NSCLC
5. last dose of systemic combination chemotherapy regimen within 21 days before Day 1 of study treatment
6. last dose of single-agent chemotherapy regimen within 14 days before Day 1 of study treatment
7. prior therapy with an experimental agent whose primary mechanism of action was inhibition of the EGFR or its associated tyrosine kinase
8. known, severe hypersensitivity to gefitinib or any of the excipients of the product
9. clinical evidence of other co-existing malignancies with exception of basal cell carcinoma
10. unable to swallow tablets
11. any unresolved chronic toxicity from previous anticancer therapy that, in the opinion of the investigator, made it inappropriate for the patient to be enrolled in the study
12. any evidence of clinically active ILD unless due to uncomplicated progressive lymphangitic carcinomatosis (patients who had chronic stable radiographic changes and who were asymptomatic did not need to be excluded)
13. absolute neutrophil counts less than 1.0x109/litre (L) or platelets less than $100x10^9$/L
14. serum bilirubin greater than 3 times the upper limit of reference range (ULRR)
15. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times the ULRR

16. in the opinion of the investigator, any evidence of severe or uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)
17. evidence of any other significant clinical disorder or laboratory finding that made it undesirable for the patient to participate in the study
18. pregnancy or breast feeding (women of child-bearing potential)
19. concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort
20. treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment

Criteria for Patient Discontinuation from Study or Therapy:

1. voluntary discontinuation by the patient. Patients were free to discontinue their participation in the study at any time, without prejudice to further treatment.
2. safety reasons as judged by the investigator and/or AZ
3. severe non-compliance to the study protocol as judged by the investigator and/or AZ
4. incorrect enrolment or randomization of the patient (unless patient was benefiting from protocol therapy)
5. death
6. patient lost to follow-up
7. patient no longer derived clinical benefit according to the treating investigator (radiological progression did not necessarily lead to discontinuation of study therapy)

Treatment Agents:

Table 12: Investigational agent use (Source: ISEL CSR and Protocol; Reviewer Table)

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Schedule
Gefitinib	250 mg tablets	AstraZeneca	F012653	Daily
Placebo	Placebo size matched	Tablets	F012647	Daily

Statistical Plan:

The primary analysis compared overall survival of gefitinib 250 mg to placebo. This analysis was performed on the ITT population. The treatment arms were compared with a log-rank test stratified for the factors of histology (adenocarcinoma versus other), gender (male versus female), smoking history (never smoked versus current/former smoker), reason for prior chemotherapy failure (refractory versus intolerant), number of

prior chemotherapy regimens (1 versus 2 regimens), performance status (0 or 1 versus 2 or 3).
This model was fitted to the adenocarcinoma population as well as to the overall population. Supportive Cox regression analyses were also conducted, per protocol, with covariate adjustment using the same factors as specified for the log-rank test. In order to control the overall type-I error rate, Hochberg's procedure (Hochberg 1988, Tamhane and Dunnett 1999) was to be used to assess the significance of the results in the two co-primary populations; if both populations yielded p-values of 0.05 or less for survival, this maintained the overall type-I error rate at 5%. However, if the larger of the two p-values exceeded 0.05, the lower p-value was assessed at the p=0.025 level to maintain an overall type-I error rate at 5%.

Table 13: Key protocol amendments (Source: ISEL CSR and Protocol; Reviewer Table)

Number (date)	Key details of amendment	Reason for amendment	Persons who initiated amendment
1 23 April 2003	Wording detailing the stratification of patients was amended to include tumor histology (adenocarcinoma versus other) and gender (male versus female), while race (Asian versus other) and prior number of chemotherapy regimens (1 versus 2) were removed. In addition, histology (adenocarcinoma versus other) was included as a stratification factor in the secondary analysis. Several editorial changes were also made to the protocol as part of this amendment; however, none of these impacted on the study design or patient safety	The stratification factors were changed following advice from FDA	Clinical Study Team Leader
2 14 July 2004	Data from the BR-21 study of erlotinib versus placebo in patients with recurrent NSCLC who had failed at least one prior chemotherapy regimen (Shepherd et al 2004) showed a significant survival advantage for erlotinib that was independent of histology. In the light of these data, the IDMC recommended that: • the overall population be included as a coprimary population alongside the adenocarcinoma population • the interim analysis should be conducted at the close of recruitment and the final analysis should be performed once 900 deaths had accrued in the overall population.	To enable the IDMC recommendations to be implemented	Study statistician
	Study plan was amended to include safety assessments (SAE collection) in patients who were ongoing after data cut off	To fulfil safety reporting requirements for patients who were still receiving study therapy post-data cut off.	Clinical Study Team Leader
	The text was changed to state that patients who were ongoing at data cut off should be monitored by the Investigator as per normal local practice and that SAEs only should be collected	To allow assessments to be carried out on patients who were ongoing post-data cut off.	Clinical Study Team Leader

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Proposed indication: IRESSA is indicated 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

6.1.1 Methods

The analysis of efficacy for gefitinib was based on the single arm IFUM study where patients were prospectively selected for activating sensitive EGFR mutations. The approval was supported by retrospective subgroup analysis based on EGFR mutation status from the IPASS study.

IFUM:
The first patient was screened for the study on 8 September 2010, and the last patient started study treatment (gefitinib) on 15 February 2012. The date for the data cut off (DCO) was defined as 6 months (15 August 2012) after the last patient had started treatment. After DCO, all patients remaining in the study were contacted to confirm survival status. Last survival contact was performed on 6 September 2012. Dr. Kazandjian completed both the efficacy and safety review. Statistical results were confirmed with the statistical reviewer Dr. Yuan.

6.1.2 Demographics

The demographics in general was similar to that of a US based trial. A variety of age groups were enrolled.

Figure 17: Age of patients enrolled (Source: IFUM Dataset; Reviewer Figure)

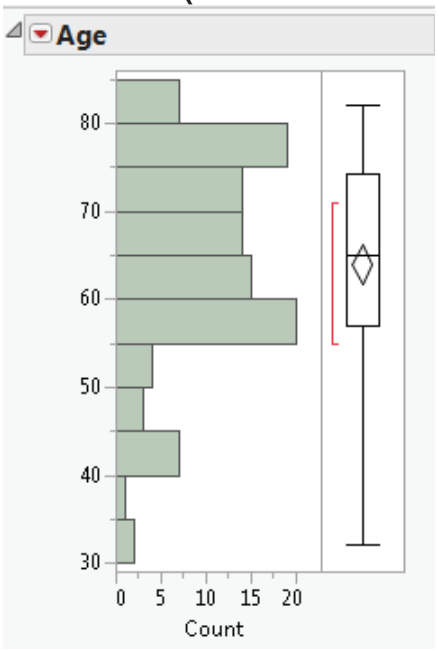


Table 14:Disease characteristics for IFUM (Source: IFUM Dataset; Reviewer Figure)

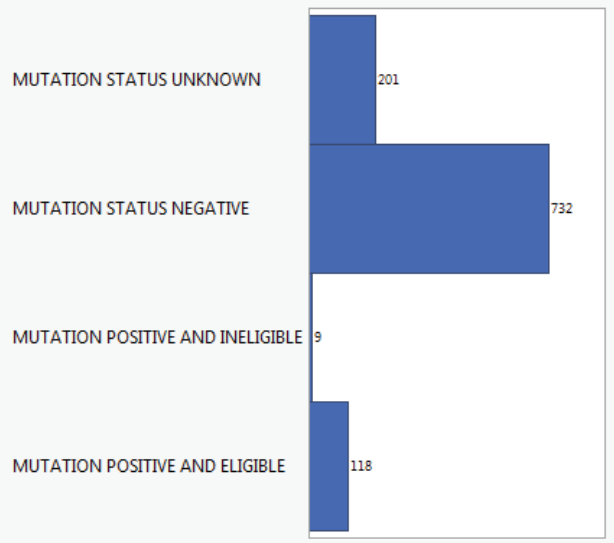
Demographic & Characteristics Safety population n=107		Gefitinib
Age	Median	65
Sex	Female	71%
Race	White	100%
Smoking	Never Former Current	64% 30% 6%
Histology	Adenocarcinoma	97%
Stage	IIIa IIIb IV	1% 4% 95%
ECOG PS	0 1 2	45% 48% 7%
Mutation	Exon 19indel L858R L861Q G719X Exon 20 ins. (insens)	65.1% 31.1% 1.9% 1.9% n/a

Reviewer Note: As shown by the demographics of the study and as expected by enrollment criteria, all patients were Caucasian. Most patients were female and ECOG status of 0-1.

6.1.3 Subject Disposition

A total of 1060 patients with locally advanced or metastatic NSCLC were screened, of whom mutation status was unknown for 201, 732 were EGFR mutation negative (M-), 9 were EGFR mutation-positive (M+) but ineligible, and 118 patients were EGFR (M+) and eligible (Figure 18).

Figure 18: Characteristics of the 1060 screened patients (Source: IFUM Dataset; Reviewer Figure)



Of the 118, 11 EGFR M+ patients were not started on gefitinib treatment due to the following (Figure 19):

- 3 patients had died
- 2 patients withdrew consent
- 5 patients were withdrawn due to eligibility criteria not fulfilled
- 1 patient was withdrawn due to AE of AST increased and ALT increased

The remaining 107 patients received gefitinib, however, one patient with an exon 20 insertion mutation was incorrectly enrolled and received gefitinib for 22 days.

- 1 patient was withdrawn due to severe non-compliance to protocol

Therefore the efficacy population for this this trial includes 106 patients while the safety population includes 107 patients.

Figure 19: Disposition of EGFR Mutation positive patients (Source: IFUM Dataset; Reviewer Figure)

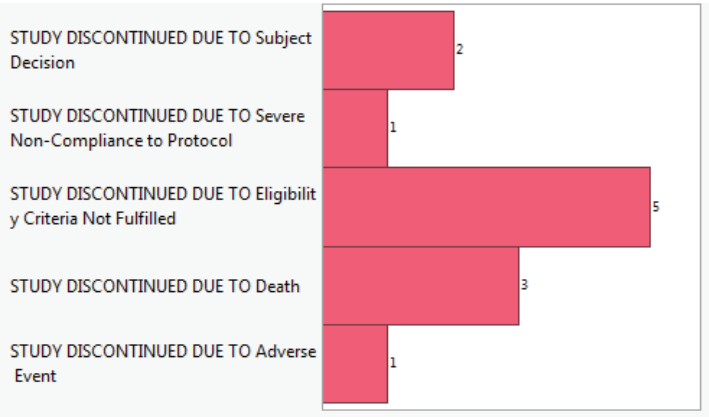


Figure 18 shows the overall disposition of patients. At the time of data cut-off approximately half of the patients were still on treatment.

Figure 20: Overall disposition of patients (Source: IFUM Dataset; Reviewer Figure)

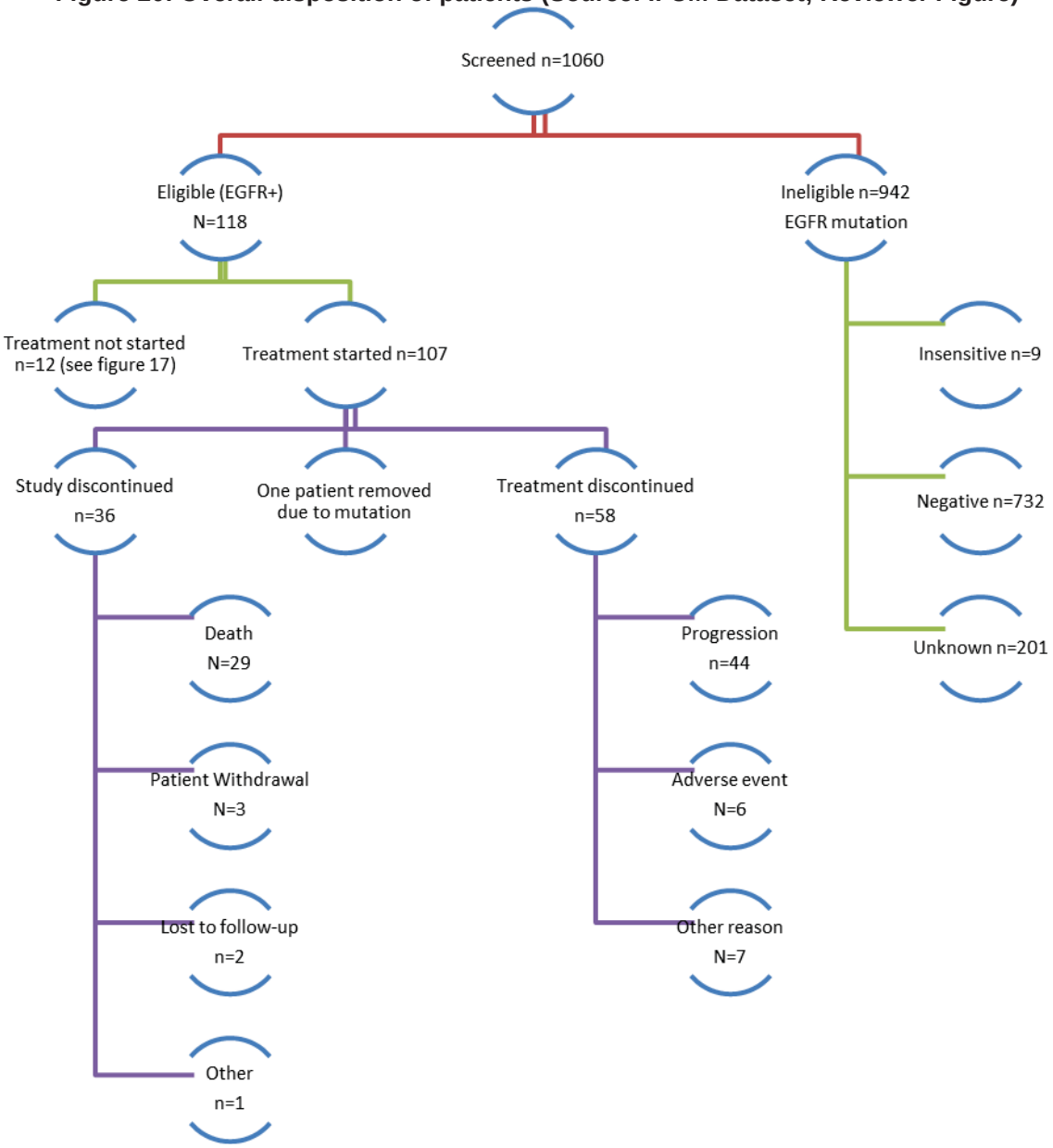
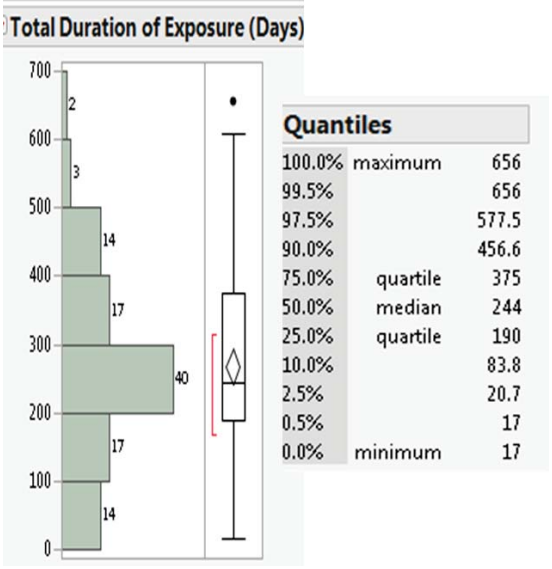


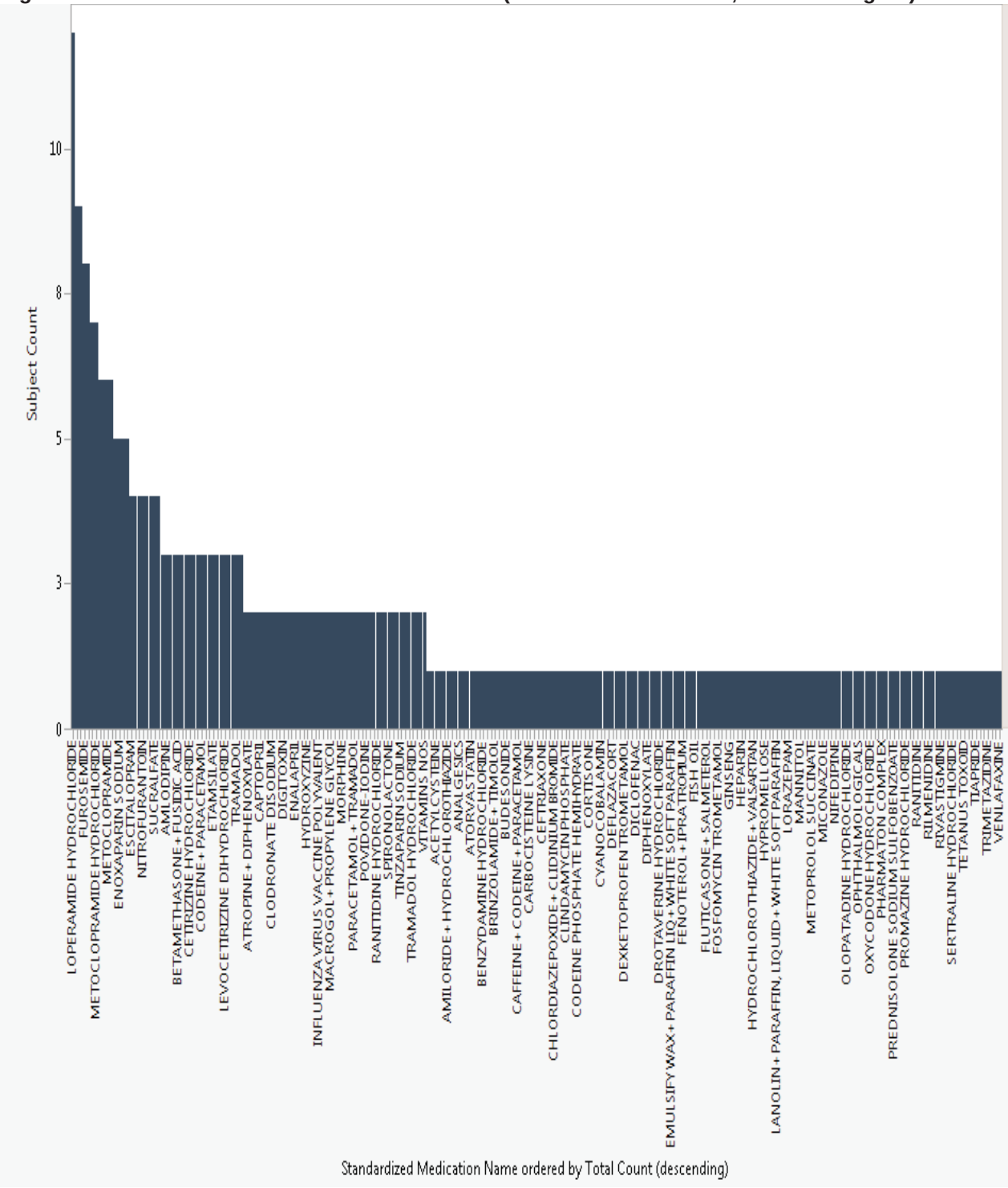
Figure19 shows the duration of treatment. Most patients received between 200-300 days (mean: 267 days) of treatment (6.5-10 months).

Figure 21: Duration of treatment exposure (Source: IFUM Dataset; Reviewer Figure)



The following figure demonstrates the variety of concomitant medications used.

Figure 22: Concomitant medication used in IFUM (Source: IFUM Dataset; Reviewer Figure)



Interestingly, a few patients received other anti-cancer treatment which mostly included radiation therapy.

Figure 23: Patients receiving concomitant other cancer treatments (Source: IFUM Dataset; Reviewer Figure)

Reviewer Note: Outside of one patient receiving carboplatin/pemetrexed, the remainder received radiation therapy. In the case of the patient receiving carboplatin/pemetrexed, this occurred after progression and the two therapies were not given concurrently. In the case of patients receiving radiotherapy, two patients received concurrent radiotherapy. The efficacy endpoint time variables used were based on progression while on gefitinib, and therefore this is unlikely to confound the primary endpoint of ORR but might confound OS.

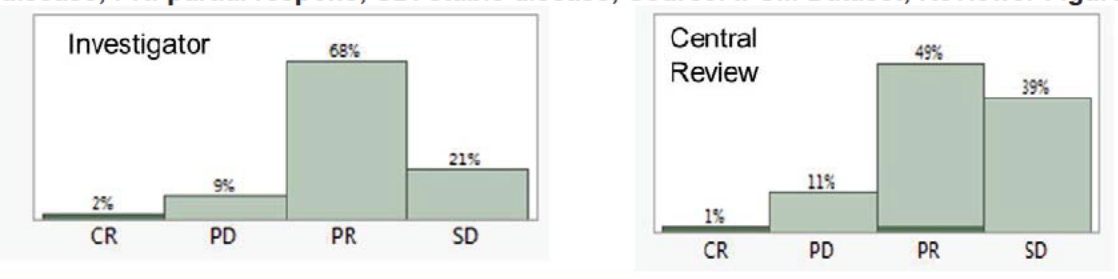
6.1.4 Analysis of Primary Endpoint(s)

The study date of analysis for the data lock was 6 months after the last patient was enrolled. The primary objective was ORR based on investigator assessment. This ORR was 70% (95%CI: 60.5, 77.7) see table 14. The duration of response for this group was 8.3 months (95%CI: 40.6, 59.4) which is fairly durable. The specific best attained responses can be seen in figure 21.

Table 15: Primary endpoint of ORR (Source: IFUM Dataset; Reviewer Table)

	ORR	95%CI	DoR	95%CI
Investigator	69.8%	60.5,77.7	8.3 mths	7.6, 11.3
IRC	50.0%	40.6,59.4	6.0 mths	5.6, 11.1

Figure 24: Distribution of best achieved response (CR: complete response; PD: progressive disease; PR: partial respone; SD: stable disease; Source: IFUM Dataset; Reviewer Figure)



Reviewer Note: The discrepancy between investigator and central review was approximately 20%. If one takes the lower ORR, it is still clinically significant. However, FDA asked the sponsor to clarify the discrepancy and the following represents that information request.

In Study IFUM, there was a discrepancy between ORR by investigator and IRC. In 17 cases, patients were determined to be "non-measurable" according to the Independent Radiology Review (IRR) assessment but not by the investigator. The Applicant stated that in 16 of the 17 patients, the information from at least 1 of the central reviewers indicated the presence of multiple nodules within the lung (bilaterally in 14 patients and in the left lung only in 2 patients). In addition, 12 of the 16 patients had accompanying pleural fluid or pleural effusion as assessed by at least 1 central reviewer. Based on the data available (tumor site and size), the Applicant's explanation is that while

investigators measured multiple lung nodules as target lesions the IRR considered them non-target lesions.

Other minor discrepancies included 2 patients that had metastases from the lung that were unusual (lesions in the thyroid [10 mm] and pancreas [40 mm], respectively), which while noted by the investigator were not identified by the central reviewers. In addition, 2 patients had target lesions (in the adrenal glands and lung) that were identified by the investigators and also confirmed by 1 of the independent reviewers; however, there was disagreement between the 2 independent reviewers. The central review adjudicator made a decision based on the overall assessment including the baseline assessment of target lesions and follow-up assessments. The agreement between the investigator and 1 of the reviewers had no bearing on the judgment of the adjudicator. The table below summarizes the differences.

Table 16: Comparison of Investigator determined response and independent review determined response (Source: IFUM Dataset; Reviewer Table)

Investigator	IRR	# of discrepancies
CR	PR	1
PD	PR	1
PD	SD	1
PR	PD	4
PR	SD	25
SD	PR	7

If these 17 cases are excluded from the analysis for not having measurable disease in a sensitivity analysis, the responses rate per IRR becomes:

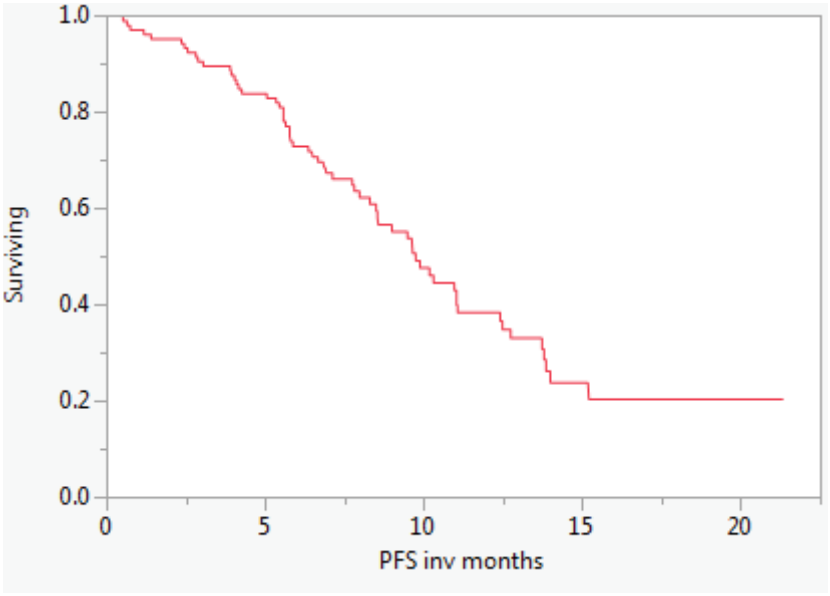
Table 17: Exploratory ORR based on independent review and excluding unevaluable patients (Source: IFUM Dataset; Reviewer Table)

	N	Objective Responders	Response Rate %	95% Confidence Interval
Excluding patients with no measurable disease at baseline according to central review	89	53	59.6	(49.2, 69.1)

6.1.5 Analysis of Secondary Endpoints(s)

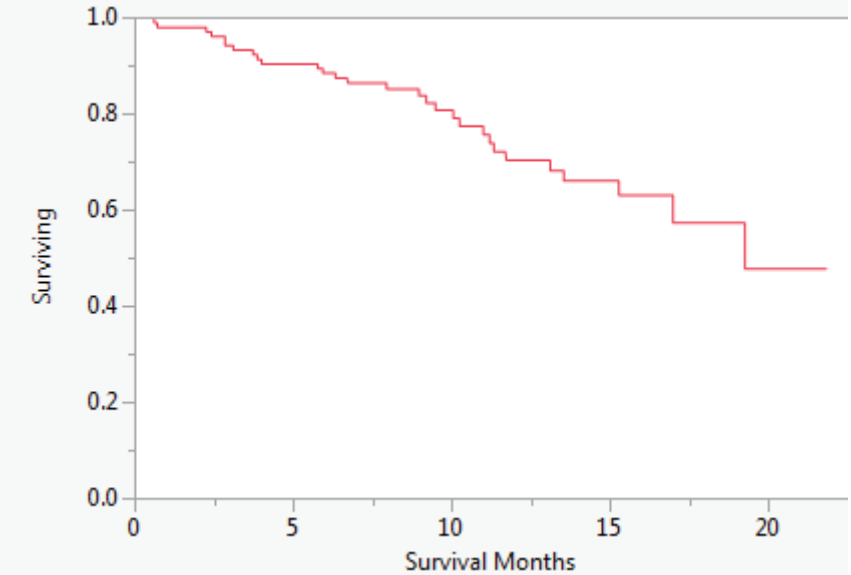
Secondary endpoints included progression free survival (PFS) and overall survival (OS). Median PFS by Investigator was 9.7 months (95% CI: 8.5, 11.0) and Kaplan Meier curve is shown below.

Figure 25: IFUM Kaplan Meier Curve of PFS by Investigator (Source: IFUM Dataset; Reviewer Figure)



The median OS was 19.22 months (95% CI:15.2, NA)

Figure 26: OS in IFUM (Source: IFUM Dataset; Reviewer Figure)



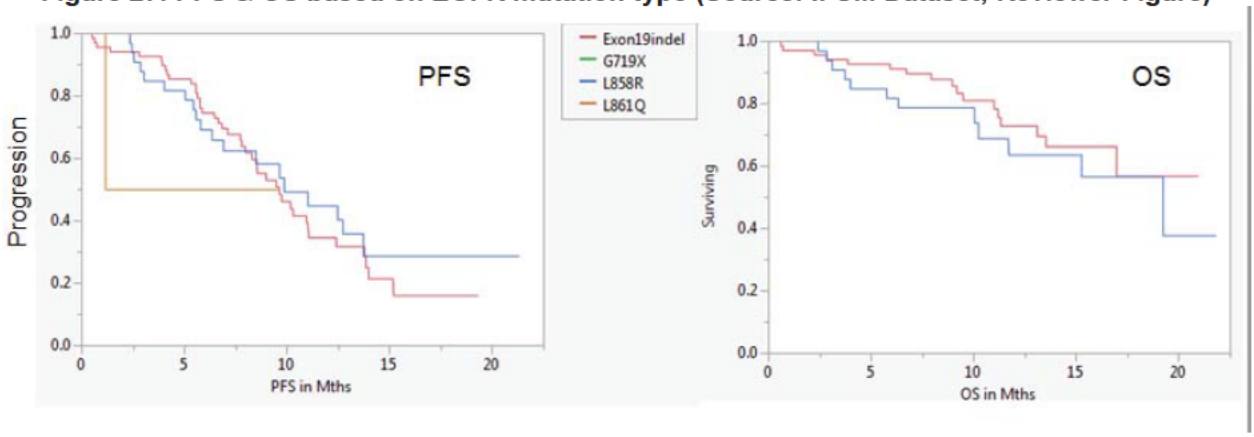
6.1.6 Other Endpoints

Efficacy was also evaluated based on EGFR mutation type.

Table 18: Responders and median DoRs based on EGFR mutation subtype (Source: IFUM Dataset; Reviewer Table)

Mutation	Responders	ORR	mDoR months (Range)
Ex19indel	50 of 69	72%	8.3 (2.6, 17.7+)
L858R	21 of 33	64%	8.3 (2.6, 14.1+)
L861Q	1 of 2	-	2.8+
G719X	2 of 2	-	2.8+ & 5.6+

Figure 27: PFS & OS based on EGFR mutation type (Source: IFUM Dataset; Reviewer Figure)



6.1.7 Subpopulations

Table 19: Demographic subgroup analysis of ORR and DoR (Source: IFUM Dataset; Reviewer Table)

	ORR	DoR median
Overall	70%	8.3 months
Male Sex	68%	8.3 months
Female Sex	71%	9.6 months
Age ≤ 65 yo	65%	9.7 months
Age > 65 yo	75%	8.3 months
ECOG=0	75%	8.3 months
ECOG=1	65%	8.8 months
ECOG=2	71%	12.5 months

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Clinical Pharmacology Review

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

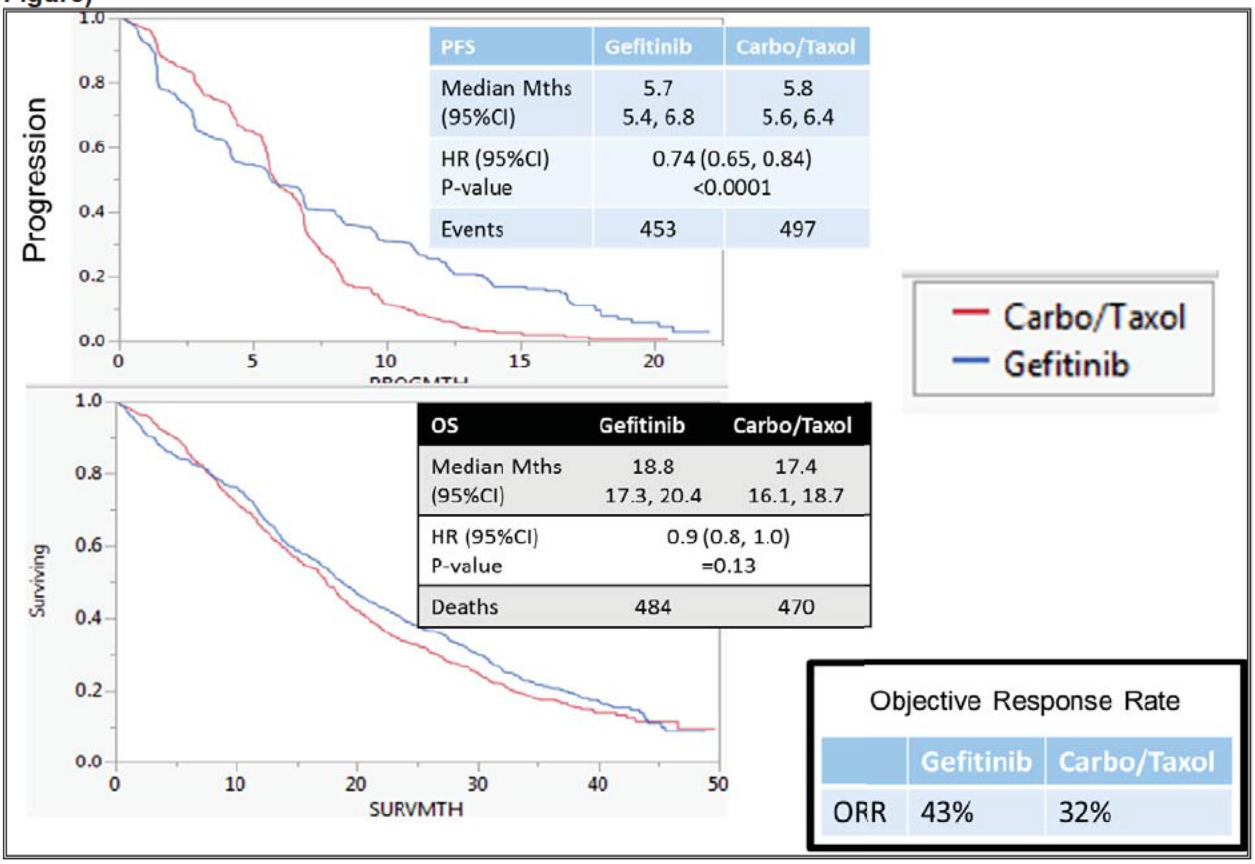
Results from the single arm IFUM study were supported by the retrospective analysis of the EGFR mutation subgroups in the IPASS study. The following table shows the patient baseline and disease characteristics.

Table 20: IPASS unselected patient and disease characteristics (Source: IPASS Dataset; Reviewer Table)

Demographic & Characteristics ITT population n=1217 Safety population n=1196 (represented below)		Gefitinib	Carboplatin/ Paclitaxel
Age (years)	Median	57	57
Sex	Female	79%	79%
Race	Asian	99%	100%
Smoking	Never Light Ex Smoker	94% 6%	93% 7%
Histology	Adenocarcinoma Bronchoalveolar	96% 4%	98% 2%
Stage	Metastatic Locally advanced	75% 25%	76% 24%
ECOG PS	0 1	26% 64%	27% 63%
EGFR Mutation (retrospectively collected)	Unknown Negative Exon 19indel L858R L861Q G719X Insensitive	63% 15% 10% 10% 0 0.002% 1.2%	64% 14% 12% 7% 0.003% 0.003% 1.5%

In the ITT population who were selected based on clinical characteristics and not EGFR mutation status, the primary endpoint was investigator derived PFS. The figures below show the PFS, OS, and ORR in the ITT population.

Figure 28: IPASS endpoints of PFS, OS, and ORR N=1217 (Source: IPASS Dataset; Reviewer Figure)



Reviewer Note: This study met its primary endpoint of PFS. However, as seen by the KM plots, the arms cross over around month 5. This is most likely due to a subset of patients who were not benefiting from gefitinib early on (likely due to not having sensitizing EGFR mutations). Therefore, as discussed below, a retrospective exploratory subgroup analysis was performed.

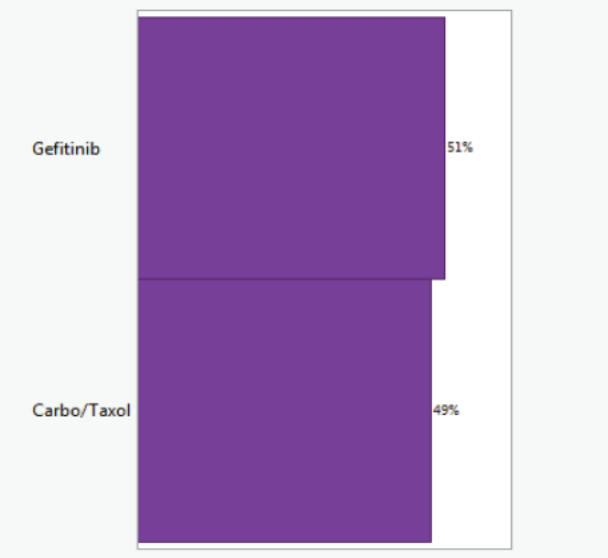
Of the 1,217 patients randomized to the two arms, 85% of patients had consented to biomarker analysis in order to collect EGFR status information. Of the 1,217, 56% provided samples and 36% (437) of these had evaluable results. This was due to 118 being cytology samples (unevaluable with the technology used) and 128 histology samples were either of insufficient quality for analysis or had other issues. Based on the information request sent to the Applicant, the following information was given regarding the unevaluable samples (table below).

Table 21: Number of patients and reasons for unevaluable samples (Source: IPASS Dataset and Applicant response to information request; Reviewer Table)

Reason unevaluable	Overall n	Gefitinib n	Chemotherapy n
Failed pathology review	98	54	44
Cytology sample	118	63	55
Insufficient DNA	10	6	4
Assay failed	4	1	3
Information not evaluable	16	10	6

The distribution of patient samples tested were balanced between the arms and shown in the figure below.

Figure 29: Sample EGFR testing balanced between the arms (Source: IPASS Dataset; Reviewer Figure)

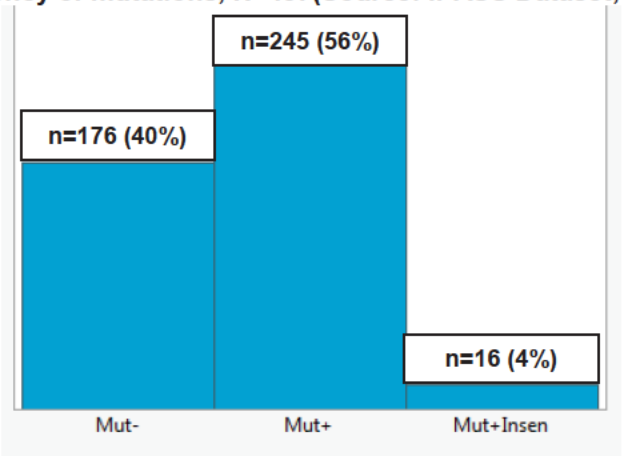


Reviewer Note: A major reason for samples being unevaluable was because they were cytology samples. As the EGFR assay is not established for use on these samples, this appears to be reasonable. Regardless, the overall percentage of patients tested between arms appears to have been balanced, limiting further bias.

Those samples with mutations were divided into mutations thought to be sensitive to drug (sensitive mutations = G719X, L858R, exon 19 deletions, L861Q and L858R/Exon19del) and those not (insensitive mutations = Exon 20 insertional, T790M

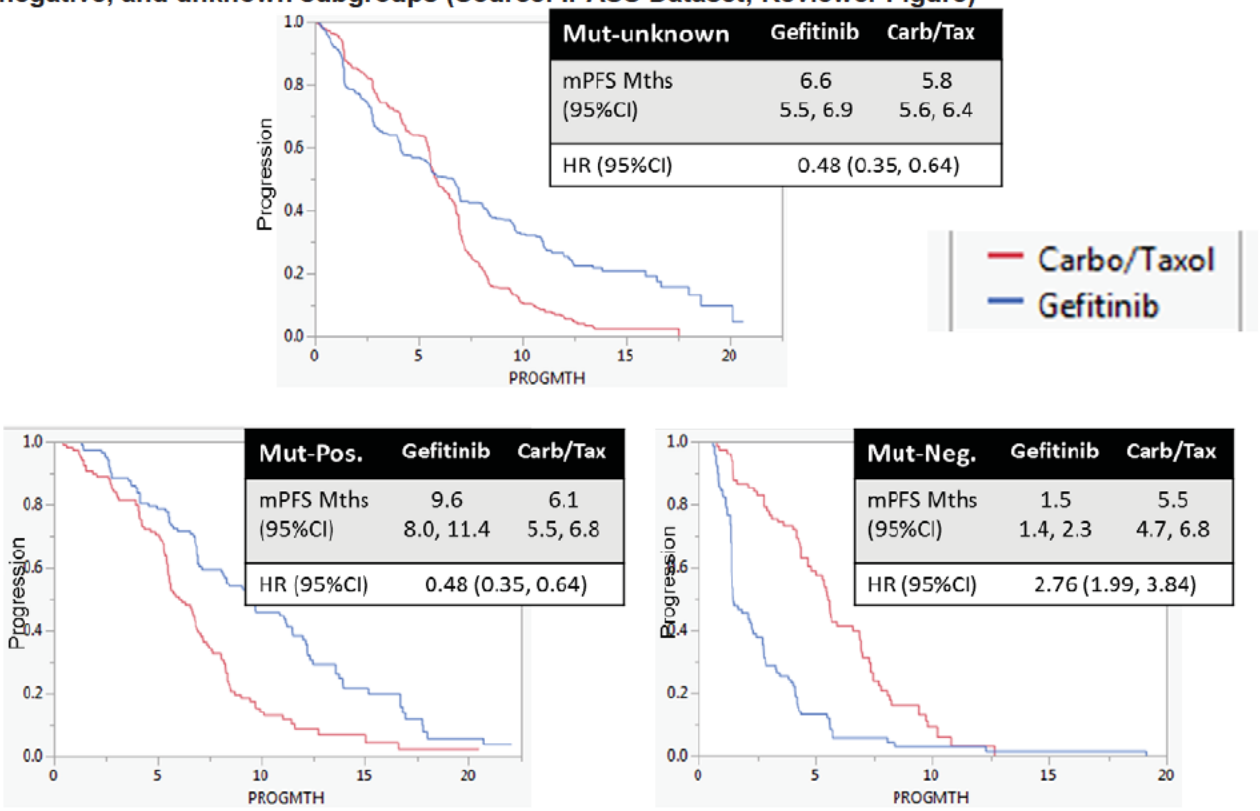
point mutations and compound mutations of Exon19 deletion/T790M and L858R/T790M) The figure below shows the mutation status of samples tested.

Figure 30: Frequency of mutations, N=437(Source: IPASS Dataset; Reviewer Figure)



Subgroup analysis were performed based on EGFR mutation and Kaplan Meier analysis shows the differences in efficacy compared to EGFR status and in the original ITT population.

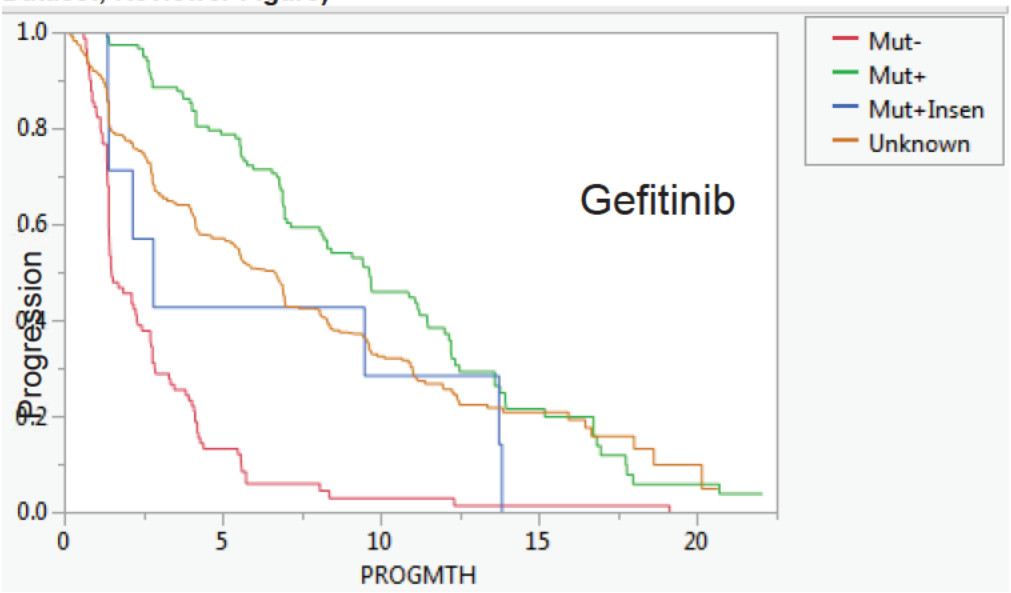
Figure 31: Kaplan Meier PFS exploratory efficacy analysis based on specific EGFR positive, negative, and unknown subgroups (Source: IPASS Dataset; Reviewer Figure)



Reviewer Note: As mentioned previously, the analysis on the ITT population shows a crossing of the arms. This is eliminated in the subgroup analysis which clearly shows that patients with a sensitizing EGFR mutations benefited in PFS with gefitinib compared to chemotherapy, however, patients without the appropriate EGFR mutation, benefited more from chemotherapy.

Further retrospective analysis was performed on the gefitinib arm to evaluate PFS based on the specific EGFR mutation.

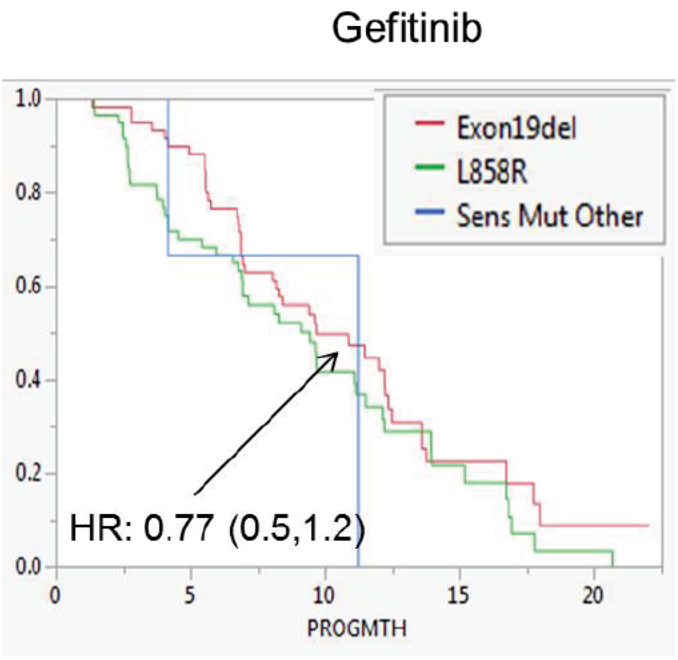
Figure 32: Exploratory efficacy on the gefitinib arm based on mutation type (Source: IPASS Dataset; Reviewer Figure)



mPFS Mths
1.4
8.0
1.3
5.5

Reviewer Note: The above figure shows that patients with a sensitive mutation had more benefit than those with activating but insensitive mutations such as T790M point and exon 20 insertion mutations. Patients who were mutation negative clearly had the worst outcome.

Figure 33: Exploratory efficacy based on type of sensitive mutation (Source: IPASS Dataset; Reviewer Figure)



Reviewer Note: This exploratory analysis suggests that there appears to be no difference in PFS based on type of sensitive mutation

The table below shows EGFR status and RECIST response in an exploratory analysis of the prospective IFUM study and the retrospective IPASS study.

Table 22: Exploratory efficacy results: Rare mutations, RECIST response, and DoR on gefitinib from IFUM and IPASS efficacy trials (Source: IPASS Dataset; Reviewer Table)

Mutation	Responders: IFUM (%)	Median DoR IFUM	Responders: IPASS	Median DoR IPASS
Ex19indel	50 of 69 (72%)	6.6 months	52 of 61 (85%)	7 months
L858R	21 of 33 (64%)	8.1 months	62 of 104 (60%)	6.9 months
L861Q	1 of 2	2.8 months	0 of 0	n/a
G719X	2 of 2	2.8 and 5.6 months	0 of 1	n/a
Exon19del/T790M	0	n/a	3 of 3	8.2, 12.5, and 12.6 months
L858R/T790M	0	n/a	0 of 1	n/a
T790M	0	n/a	0 of 1	n/a
Exon20ins	0	n/a	0 of 2	n/a

Reviewer Note: Although, the amount of enrolled patients with rare mutations is very limited, there appeared to be some activity in L861Q and G719X subtypes based on IFUM and compound heterozygous mutation Exon19del/T790M based on IPASS.
Addendum: Subsequent to an information request, the table below was submitted by the Applicant which mirrors the above analysis.

Table 23: Table submitted by the Applicant showing responses (exploratory) of rare EGFR mutations to gefitinib (Source: IPASS Dataset and Applicant response to Information Request; Applicant Table)

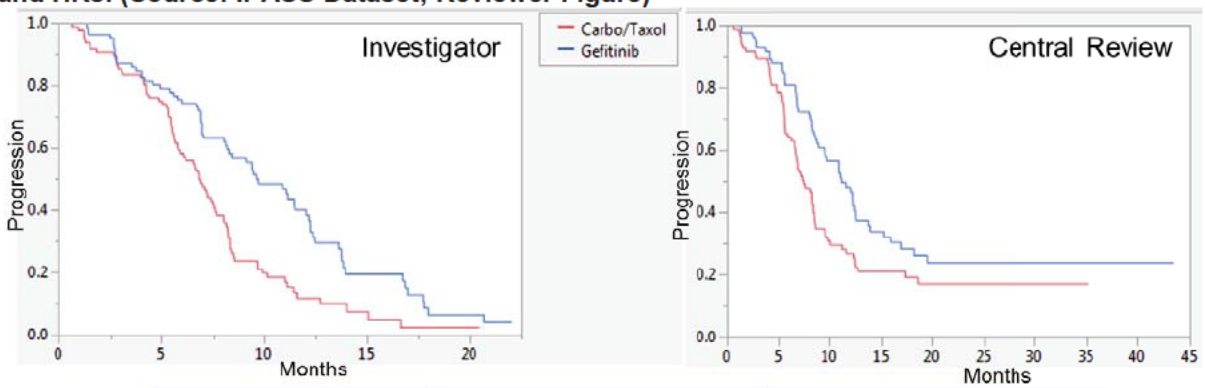
Table 2 Summary of objective responses based on investigator assessment in gefitinib studies in patients with uncommon mutations

Mutation subtype	Number of patients treated with gefitinib (in IPASS, IFUM and NEJ002)[a]	Number of patients with a partial response	PFS
Exon 19 deletion +T790M	3	3	9.5 to 13.8 months
L858R+T790M	1	0	2.8 months
G719X	6	2	0.5 to 11.2 months[c]
L861Q[b]	5	2	6.4 to 10.6 months[d]
T790M	2	0	1.4 to 2.1 months

[a] Eight patients from IPASS, 4 patients from IFUM and 5 patients from NEJ002.
[b] One patient identified as L861Q in ad-hoc analysis of IPASS samples (Yang et al 2014).
[c] Includes 2 censored observations.
[d] Includes a censored observation.
IFUM IRESSA Follow-Up Measure; IPASS IRESSA Pan-Asia Study; NEJ North East Japan; PFS Progression free survival.

As stated previously, the IPASS trial's primary endpoint was investigator determined PFS. To support investigator determined radiographic reviews, the Applicant conducted an IRR of scans from patients who had EGFR+ tumors. Of the 261 patients who qualified based on having a sensitizing EGFR mutation, central review was performed for 186 (71%). Per the Applicant, A Fisher's exact test revealed no significant differences between patients included or not included in the Central Review for any of the 3 pre-specified covariates.

Figure 34: PFS of EGFR+ patients, investigator vs. central review exploratory Kaplan-Meier curves and HRs. (Source: IPASS Dataset; Reviewer Figure)



	Investigator	Central Review
mPFS (95% CI) • Gefitinib • Carbo/Taxol	 9.5 months (7.1, 11.2) 6.3 months (5.6, 7.0)	 11.1 months (8.8, 12.5) 7.5 months (6.7, 8.4)
HR (95% CI) • P-value	0.50 (0.38, 0.67) <0.0001	0.62 (0.44, 0.89) =0.009

Reviewer Note: This analysis using IRC assessed PFS, compared to investigator, reassures the positive benefit of gefitinib vs. chemotherapy on PFS. In fact, the absolute difference between the arms favoring gefitinib using central review is 3.6 months vs. 3.2 months for IRC. Using central review, gefitinib treatment suggests a 38% decrease in the relative risk of progression over carboplatin/paclitaxel doublet treatment.

7 Review of Safety

Safety Summary

The primary analysis of safety was based on the ISEL study, a randomized, multicenter, double-blind, placebo-controlled trial of 1692 patients receiving second- or third-line treatment for metastatic NSCLC; 1129 patients received IRESSA 250 mg daily and 563 patients received placebo. The median duration of treatment with IRESSA was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), Caucasian (75%), Asian (21%), NSCLC adenocarcinoma histology (48%), never smoker (22%), ECOG PS 0 or 1 (65%), and two or more prior therapies (51%).

The pooled safety database from the three randomized trials (IPASS, INTEREST, and ISEL) was used to evaluate for serious and uncommon adverse drug reactions. Common adverse reactions were evaluated in ISEL. The most frequent adverse reactions (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 were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%). Approximately 5% of patients discontinued treatment for adverse reactions. The most frequent adverse reactions that led to discontinuation were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

Based on the data provided by the applicant, the safety profile of gefitinib in patients with metastatic EGFR+ NSCLC is acceptable.

7.1 Methods

The primary analysis of safety for gefitinib for the proposed indication was based on ISEL in previously treated patients with EGFR+ metastatic NSCLC with supportive safety data from IPASS. IPASS was an actively controlled with chemotherapy first-line treatment study in patients with metastatic NSCLC and specific clinical markers. The pooled analysis for safety was conducted on the three randomized trials, ISEL, INTEREST, and IPASS.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

ISEL was a randomized, double-blind, placebo-controlled, parallel-group, international, multicenter study, designed to assess whether the addition of gefitinib to best supportive care (BSC) in patients with previously treated locally metastatic NSCLC conferred an overall survival advantage over placebo plus BSC. Patients received the BSC available as judged by the treating investigator and were randomized to receive either gefitinib or placebo in a 2:1 ratio. The table below shows baseline patient and disease characteristics.

Table 24: ISEL study characteristics (Source: ISEL Dataset; Reviewer Table)

Demographic & Characteristics Safety population		Gefitinib N=1126	Placebo N=562
Age	Median	62	61
Sex	Female	32.6%	32.9%
Race	White	74.7%	76.6%
Smoking	Never	22.1%	22.2%
Histology	Adenocarcinoma	45.3%	45.3%
Stage	IV	47.5%	50.1%
ECOG PS	0 1 2	12.4% 53.0% 29.4%	12.4% 56.5% 25.8%

7.1.2 Categorization of Adverse Events

Safety and tolerability assessment in ISEL and the supportive studies was based on frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments and vital sign measurements. Adverse events were originally coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.1 and subsequently the Applicant updated some of the data to version 17.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. Adverse events and laboratory values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 2.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The studies ISEL, INTEREST, and IPASS were used to pool data across clinical studies. All three of these studies were randomized controlled trials. In ISEL, patients were randomized to either gefitinib or placebo, in INTEREST patients were randomized to either gefitinib or docetaxel, and in IPASS patients were randomized to either gefitinib or carboplatin/paclitaxel. The table below shows the adverse drug reactions for gefitinib across these studies. Pooled data from the integrated summary of safety data sets were reviewed and significant adverse events were checked against datasets.

7.2 Adequacy of Safety Assessments

Reviewer Note: The safety analysis was performed on the safety population that included all patients enrolled who received at least one dose of each study drug excluding those who received both (4 patients). My analyses will primarily involve this population. Additionally, unless otherwise noted, all the analyses on AEs involves all-cause or treatment emergent AEs.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In ISEL, the majority of patients experienced one or more AEs. The frequency of SAEs or CTC grade 3 or 4 AEs were similar between the groups. The frequencies of AEs leading to discontinuation or death were low in both treatment groups.

Table 25: Incidence of AEs and dose modifications in ISEL (Source: ISEL CSR; Reviewer Table)

	Gefitinib n (%)	Placebo n (%)
Patients with AEs	927 (82.3)	397 (70.6)
Grade 3 or 4 AEs	341 (30.3)	151 (26.9)
Serious AEs	216 (19.2)	98 (17.4)
AE leading to discontinuation	61 (5.4)	13 (2.3)
AE leading to death	55 (4.9)	22 (3.9)

Duration of exposure was similar in both arms with a median of 87 days of exposure for gefitinib and 81 days for placebo. Dose interruptions are presented in the table below.

Table 26: Gefitinib and placebo dose interruptions (Source: ISEL CSR; Reviewer Table)

	Gefitinib 250 mg (N=1126) N (%)	Placebo (N=562) N (%)
Any interruption		
• Adverse event	123 (10.9)	27 (4.8)
• Dose forgotten, tablets lost	91 (8.1)	45 (8.0)
• Other	55 (4.9)	25 (4.4)

In the efficacy IFUM study, approximately 94% of patients experienced at least 1 AE during the study and 15% experienced CTCAE Grade ≥3, and 19 experienced SAEs, including events with outcome of death, and 8% experienced AEs that led to discontinuation of gefitinib. Five patients (5%) died due to AEs; however, none were considered attributable to gefitinib by the investigator.

7.2.2 Explorations for Dose Response

Please see Clinical Pharmacology/ Pharmacometrics Reviews. In brief, exposure-safety relationship was noted for pneumonitis. Their analysis based on an observational study in Japanese NSCLC patients indicated that a higher risk of ILD may be associated with higher exposure to gefitinib. Additionally, it was noted by the reviewers that hepatic impairment was associated with increased levels of gefitinib. Specifically, in a study of subjects with hepatic impairment due to cirrhosis, exposure to gefitinib was approximately 1.4-, 3.6-, and 2.7-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively.

7.2.3 Special Animal and/or In Vitro Testing

Please see toxicology reviews. In brief, all nonclinical toxicology studies required to support the approval of gefitinib were previously reviewed under NDA 21399. The Applicant has submitted limited new pharmacology studies to support the mechanism of action of gefitinib in the intended patient population. Per these reviewers, there are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of gefitinib.

7.2.4 Routine Clinical Testing

In ISEL, routine laboratory tests completed at the study center included hematology (hemoglobin, platelet count, white blood count, and absolute neutrophil count, chemistry (Total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, sodium, potassium, calcium, phosphate, blood urea nitrogen, uric acid, and magnesium), coagulation (INR), and urinalysis (hematuria and protein). Hematology and chemistry parameters were checked at screening and at every cycle.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review for more information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The two similar drugs in this drug class are erlotinib and afatinib. All three of these have similar adverse event profiles; however, it appears from this review that gefitinib has a decreased incidence of adverse reactions, likely because it is dosed at the optimal biologic dose rather than at the MTD, and because it is a reversible EGFR inhibitor. These drug class AEs include diarrhea, emesis, and skin reactions.

7.3 Major Safety Results

The table below shows the incidence of major safety results.

Table 27: Major safety events from ISEL (Source: ISEL CSR; Reviewer Table)

	Gefitinib (N=1126) *N (%)*	*Placebo (N=562)* *N (%)*
All adverse events	927 (82.3)	397 (70.6)
• Treatment-related	658 (58.4)	161 (28.6)
All serious adverse events	216 (19.2)	98 (17.4)
• Treatment-related	27 (2.4)	8 (1.4)
• Non-fatal SAEs	180 (16.0)	83 (14.8)
• Deaths due to SAEs	55 (4.9)	22 (3.9)
○ Treatment-related SAE death	5 (0.4)	1 (0.2)
Discontinuations from treatment due to AEs	61 (5.4)	13 (2.3)
• Due to treatment-related AE	31 (2.8)	3 (0.5)
• Due to SAE	33 (2.9)	10 (1.8)
○ Due to treatment-related SAE	10 (0.9)	3 (0.5)
CTC Grade 3 or 4 AEs	341 (30.3)	151 (26.9)
• Treatment-related Grade 3 or 4 AEs	90 (8.0)	16 (2.8)

Reviewer Note: In this study, gefitinib was associated with a slightly increased incidence of major safety events compared to placebo.

7.3.1 Deaths

Of the 1692 patients in ISEL, 976 (57.7%) had died by the data cut-off date of 29 October 2004. Of these 976 patients, 633 (56.2%) had received treatment with gefitinib 250 mg and 341 (60.7%) had received treatment with placebo. Deaths that were related to NSCLC were lower in the gefitinib arm compared with placebo (51.3% vs. 56.8%).

Patients which were considered by the investigator to have died as a result of SAEs alone were 20 (1.8%) in the gefitinib arm and 7 (1.2%) in the placebo arm. The incidence of AEs that led to death was 55 (4.9%) in the gefitinib arm and 22 (3.9%) in the placebo arm.

Table 28: Adverse events leading to ≥1 death on gefitinib arm (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*			
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*	*P-value**
Respiratory failure	10	0.89	0	0	10.5	0.0
Pneumonia	9	0.8	3	0.53	1.5	0.8
Pulmonary embolism	6	0.53	1	0.18	3.0	0.4
Haemoptysis	3	0.27	1	0.18	1.5	1.0
Myocardial infarction	3	0.27	1	0.18	1.5	1.0
Cardiac failure	2	0.18	1	0.18	1.0	1.0
Death	2	0.18	3	0.53	0.3	0.3
Dyspnoea	2	0.18	1	0.18	1.0	1.0
Respiratory tract infection	2	0.18	0	0	2.5	1.0
Sepsis	2	0.18	1	0.18	1.0	1.0
Acute myocardial infarction	1	0.09	0	0	1.5	1.0
Acute respiratory failure	1	0.09	1	0.18	0.5	0.6
Arrhythmia	1	0.09	0	0	1.5	1.0
Cardiopulmonary failure	1	0.09	2	0.36	0.3	0.3
Cerebral ischemia	1	0.09	0	0	1.5	1.0
Cholecystitis acute	1	0.09	0	0	1.5	1.0

Gastroenteritis	1	0.09	0	0	1.5	1.0
Haemorrhage intracranial	1	0.09	0	0	1.5	1.0
Hepatic cirrhosis	1	0.09	0	0	1.5	1.0
Lung abscess	1	0.09	0	0	1.5	1.0
Metastases to meninges	1	0.09	0	0	1.5	1.0
Pulmonary oedema	1	0.09	0	0	1.5	1.0
Pulmonary sepsis	1	0.09	0	0	1.5	1.0
Respiratory arrest	1	0.09	0	0	1.5	1.0
Respiratory distress	1	0.09	0	0	1.5	1.0
Septic shock	1	0.09	1	0.18	0.5	0.6
Silent myocardial infarction	1	0.09	0	0	1.5	1.0
Staphylococcal infection	1	0.09	0	0	1.5	1.0
Thrombocytopenia	1	0.09	0	0	1.5	1.0

* p-values are exploratory in nature; RR = relative risk

The table below represents of those deaths listed in the table above which were attributable to gefitinib according to the investigator.

Table 29: Deaths due to a gefitinib-related AE per investigator (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*
Cerebral ischemia	1	0.09	0	0	1.5
Dyspnea	1	0.09	0	0	1.5
Hemorrhage intracranial	1	0.09	0	0	1.5
Hepatic cirrhosis	1	0.09	0	0	1.5
Pulmonary sepsis	1	0.09	0	0	1.5

Table 30: Narrative details of deaths due to a gefitinib-related AE per investigator (Source: ISEL CSR; Reviewer Table)

Patient	*Primary cause*	*Secondary cause*	*Related to NSCLC*	*AE PT*	*Medical Hx.*	*Time to AE onset (days)*	*Age*	*Sex*
E0620002	Cerebral ischemia	Hypertension	No	Cerebral ischemia	Concurrent hypertension	65	60	M
Patient was withdrawn due to disease progression. One week and four days after the last dose of study therapy, the patient developed CNS cerebrovascular ischemia and was admitted to hospital for treatment of a cerebrovascular accident. A brain CT scan revealed a hypodense area, most likely due to the total occlusion of the left middle cerebral artery. No treatment was administered and the patient was discharged on (b) (6) and transferred to a nursing home.								
E5303004	Acute myocardial infarction	Hepatic cirrhosis	No	Hepatic cirrhosis	Pre-existing liver cirrhosis and ascites	26	63	M
An ultrasound taken on (b) (6) showed cirrhotic changes of the liver, partially contracted gall bladder with cholelithiasis, reactive wall thickening and ascites. On (b) (6) the patient started treatment with trial therapy. On (b) (6) and four days after commencing trial therapy, the patient experienced one episode of vomiting. The patient developed gastritis and was hospitalized. On (b) (6), the patient experienced two episodes of vomiting with blood and had a blood pressure level of 180/100. Routine liver function tests revealed decreased prothrombin levels. The patient was diagnosed with hypoprothrombinemia. A liver ultrasound revealed no liver masses or bile duct dilatation, the ultrasound description was unchanged from (b) (6). A nasogastric tube was inserted and the patient experienced a massive upper gastrointestinal bleed. Simultaneously, he experienced pulmonary haemorrhage and a depressed level of consciousness, and went into a coma after endotracheal intubation due to bradypnea. The patient's rate of evolving ECG changes was highly suggestive of myocardial infarction. During the hospital stay, a CT scan showed a possible lacunar infarction otherwise unremarkable. This lacunar infarction was later found to be present since before the patient was screened into the study. Primary cause of death was acute myocardial infraction and also a result of complication of liver cirrhosis (bleeding from esophageal varices).								

E1205007	Respiratory failure	Lung neoplasm malignant	Yes	Dyspnea	Pneumonia prior to study entry with past and current history of COPD and Ischemic heart disease	19	63	M
The patient was also a smoker, having smoked 20-30 cigarettes a day since the age of 18. After two weeks and five days of study therapy, the patient was hospitalized with dyspnea, which had increased over the last few weeks (CTC grade 3). A chest x-ray showed progression of the known tumor. On the same day the CTC grade for dyspnoea was graded to 4 and the patient received treatment with prednisolone and cefuroxime.								
E1206001	Pulmonary sepsis	Lung neoplasm malignant	Yes	Pulmonary sepsis	Pulmonary embolism diagnosed prior to study entry	30	68	F
Patient was a 68 year old Caucasian female who was treated for 29 days with gefitinib, her metastatic sites of disease included adrenals, soft tissue and spleen. She discontinued therapy due to symptomatic deterioration. Her other medical history included osteoporosis and pulmonary thrombosis. Death was attributed to pulmonary sepsis due to her underlying cancer.								
E5300002	Hemorrhagic stroke	Lung carcinoma cell type unspecified stage IV	Yes	Hemorrhage intracranial	History of transient Ischemic attack and concomitantly receiving warfarin	8	62	M
The patient was receiving warfarin for his deep vein thrombosis from 21 October 2003, (1mg/day). His INR on (b) (6) was 1.13. By the (b) (6) it had increased to 1.63. The patient's dose of warfarin was changed to 1 mg/day and 2.5 mg/day on alternate days. Treatment with study therapy was started on (b) (6) and his INR on the (b) (6) was 8.16. The patient's dose of warfarin was reduced to half a tablet/day (0.5mg/day). INR continued to increase to 8.67 on (b) (6) and warfarin was discontinued on that day. Three days prior to consultation, the patient developed generalized malaise and was found to be anemic (CTC grade 3). hemoglobin level was 7.9 g/dl and he was treated with two units of packed red blood cells was administered on the same day and vitamin K was given for the prolonged prothrombin time. The patient went home following the blood transfusion and the event improved. On (b) (6) the patient developed a CNS haemorrhage (CTC grade 4) at home. Both of the patient's pupils were deviated upwards to the right. The patient was also unable to speak and subsequently became comatose. No investigations were carried out and no treatment was given for the event. His last dose of study therapy was taken on this date and he passed a week after his first dose of therapy.								

Reviewer Note: Although there were no major safety signals compared to placebo, the most frequently reported adverse events that led to death were pneumonia, pulmonary embolism, and respiratory failure. After review of narratives for deaths, it is apparent that these patients had multiple comorbidities contributing to death, including lung cancer and tobacco exposure.

7.3.2 Nonfatal Serious Adverse Events

Table 31: Serious adverse events occurring in >2 patients treated with gefitinib and > 1.5 fold difference (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*			
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*	*P-value**
Asthenia	5	0.44	0	0	5.5	0.2
Constipation	5	0.44	0	0	5.5	0.2
Pyrexia	8	0.71	1	0.18	4.0	0.3
Confusional state	3	0.27	0	0	3.5	0.6
Empyema	3	0.27	0	0	3.5	0.6
Pulmonary edema	3	0.27	0	0	3.5	0.6
Respiratory failure	12	1.07	2	0.36	3.0	0.2
Vomiting	6	0.53	1	0.18	3.0	0.4
Anemia	11	0.89	2	0.36	2.5	0.4
Diarrhea	9	0.8	2	0.36	2.2	0.4
Sepsis	4	0.36	1	0.18	2.0	1.0
Septic shock	4	0.36	1	0.18	2.0	1.0
* p-values are exploratory in nature; RR = relative risk						

Table 32: Narrow SMQ search for serious adverse events occurring in >2 patients treated with gefitinib and > 1.5 fold difference (Source: ISEL Dataset; Reviewer Table)

SMQ (Narrow Search)			*Gefitinib (N = 1126)*		*Placebo (N = 562)*		
Level 1	*Level 2*	*Level 3*	*Events*	*Prop (%)*	*Events*	*Prop (%)*	*RR*
Biliary disorders			3	0.27	0	0	3.3
Biliary disorders	Functional, inflammatory and gallstone related biliary disorders		3	0.27	0	0	3.5
Biliary disorders	Functional, inflammatory and gallstone related biliary disorders	Gallbladder related disorders	3	0.27	0	0	3.5
Cerebrovascular disorders	Central nervous system hemorrhages and cerebrovascular conditions	Ischemic cerebrovascular conditions	5	0.44	1	0.18	2.5
Gastrointestinal nonspecific inflammation and dysfunctional conditions			30	2.22	8	0.89	2.5
Acute central respiratory depression			14	1.24	3	0.53	2.3
Gastrointestinal nonspecific inflammation and dysfunctional conditions	Gastrointestinal nonspecific symptoms and therapeutic procedures		28	2.04	8	0.89	2.3
Noninfectious Diarrhea			9	0.8	2	0.36	2.2
Shock	Toxic-septic shock conditions		4	0.36	1	0.18	2.0
Cerebrovascular disorders			7	0.62	2	0.36	1.7
Cerebrovascular disorders	Central nervous system hemorrhages and cerebrovascular conditions		7	0.62	2	0.36	1.7

Table 33: Life threatening serious adverse events occurring in patients treated with gefitinib (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*			
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	RR	P-value
Pulmonary edema	3	0.27	0	0	3.5	0.6
Pneumonia	6	0.53	1	0.18	3.0	0.4
Dyspnea	4	0.36	1	0.18	2.0	1.0
Acute myocardial infarction	1	0.09	0	0	1.5	1.0
Anaemia	1	0.09	0	0	1.5	1.0
Arrhythmia	1	0.09	0	0	1.5	1.0
Cardiac failure	1	0.09	0	0	1.5	1.0
Convulsion	1	0.09	0	0	1.5	1.0
Hemiparesis	1	0.09	0	0	1.5	1.0
Hepatic cirrhosis	1	0.09	0	0	1.5	1.0
Interstitial lung disease	1	0.09	0	0	1.5	1.0
Neutropenia	1	0.09	0	0	1.5	1.0
Peripheral ischaemia	1	0.09	0	0	1.5	1.0
Respiratory failure	1	0.09	0	0	1.5	1.0
Sepsis	1	0.09	0	0	1.5	1.0
Septic shock	1	0.09	0	0	1.5	1.0
Vena cava thrombosis	1	0.09	0	0	1.5	1.0
Pleural effusion	3	0.27	1	0.18	1.5	1.0

* p-values are exploratory in nature; RR = relative risk

Reviewer Note: Frequency of SAEs was similar in both treatment groups and relatively low. The most frequently reported SAEs were pneumonia, dyspnea, pleural effusion, respiratory failure, and dehydration. The SAEs which were relatively more common in the gefitinib treated arm (> 2 times; table above) were asthenia, constipation, pyrexia, confusional state, empyema, pulmonary edema, respiratory failure, vomiting, anemia, and diarrhea. An SMQ search potentially identified a gallbladder signal. The most common (>1 patient; table above) SAE indicated as life threatening were pulmonary edema, pneumonia, and dyspnea which were likely related to the underlying cancer. Of note, there was only one case of a pneumonitis SAE.

7.3.3 Dropouts and/or Discontinuations

Overall, a total of 74 patients (4.4%) had treatment discontinuation due to an AE. AEs leading to discontinuation were 5.4% and 2.3% in the gefitinib 250 mg and placebo groups, respectively. The most commonly reported AEs leading to discontinuation were the gastrointestinal events of diarrhea, nausea and vomiting that are commonly associated with gefitinib therapy. Discontinuations due to respiratory events were slightly more common in the gefitinib 250 mg group. The table below shows adverse events leading to temporary discontinuation of gefitinib therapy.

Table 34: Any adverse event leading to temporary gefitinib discontinuation occurring in > 2 patients and > 1.5 fold difference (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	RR
Diarrhea	32	2.66	0	0	30.5
Pyrexia	7	0.53	0	0	6.5
Rash	13	1.07	1	0.18	6.0
Transaminases increased	4	0.36	0	0	4.5
Dry skin	3	0.27	0	0	3.5
Vomiting	23	1.87	5	0.71	2.6
Dyspnea	5	0.44	1	0.18	2.5

Table 35: Any adverse event leading to permanent gefitinib discontinuation occurring in > 2 patients (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	RR
Nausea	6	0.53	0	0	6.5
Vomiting	6	0.53	0	0	6.5
Diarrhea	5	0.44	1	0.18	2.5
Myocardial infarction	3	0.27	0	0	3.5
Dyspnoea	3	0.27	1	0.18	1.5
Pneumonia	3	0.27	1	0.18	1.5
Haemoptysis	2	0.18	0	0	2.5
Pneumonitis	2	0.18	0	0	2.5
Pulmonary embolism	2	0.18	0	0	2.5
Rash	2	0.18	0	0	2.5
Respiratory failure	2	0.18	0	0	2.5

Reviewer Note: Temporary and permanent gefitinib discontinuation occurred as expected for the stated adverse events. As expected, the most common causes were nausea, vomiting, and diarrhea.

7.3.4 Significant Adverse Events

The most common grade 3-4 adverse events (≥4% & ≥2 fold difference) on the gefitinib arm was ALT elevation (12.8%) and febrile neutropenia in the chemotherapy arm (9.4%) as seen in the table below.

Table 36: Most common grade 3 & 4 occurring ≥ 0.5% adverse events ≥ 1.5 fold difference (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*			
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*	*P-value**
Diarrhea	20	1.69	6	0.89	1.9	0.3
Hypotension	13	1.15	3	0.53	2.2	0.3
Respiratory failure	12	1.07	2	0.36	3.0	0.2
Vomiting	10	0.89	2	0.36	2.5	0.4
Dizziness	8	0.71	1	0.18	4.0	0.3
Abdominal pain	9	0.62	2	0.36	1.7	0.7
Atrial fibrillation	7	0.62	2	0.36	1.7	0.7
Pyrexia	7	0.62	2	0.36	1.7	0.7

* p-values are exploratory in nature; RR = relative risk

Table 37: Narrow SMQ search for grade 3 & 4 occurring ≥ 0.5% adverse events ≥ 1.5 fold difference (Source: ISEL Dataset; Reviewer Table)

SMQ (Narrow Search)			*Gefitinib (N = 1126)*		*Placebo (N = 562)*		*RR*
Level 1	*Level 2*	*Level 3*	*Events*	*Prop (%)*	*Events*	*Prop (%)*	
Hepatic disorders			14	1.07	2	0.36	3.0
Hepatic disorders	Drug related hepatic disorders - comprehensive search		14	1.07	2	0.36	3.0
Hepatic disorders	Drug related hepatic disorders - comprehensive search	Liver related investigations, signs and symptoms	10	0.71	1	0.18	4.0
Acute central respiratory depression			13	1.15	3	0.53	2.2
Noninfectious diarrhea			20	1.69	6	0.89	1.9

Reviewer Note: Grade 3 and 4 AEs in the gefitinib arm are consistent with the identified adverse events. However, overall the incidence is low compared to placebo. The SMQ search identified hepatic disorders; however, this has been previously identified.

7.3.5 Submission Specific Primary Safety Concerns

Important safety events of interest were interstitial lung disease (ILD) and ocular disorders. ILD occurred in 1.1% of gefitinib treated patients and 0.9% of placebo treated patients. Grade 3 or 4 ILD occurred in 6 (0.5%) of gefitinib treated patients and 4 (0.7%) of placebo treated patients. Ocular events slightly increased with gefitinib were conjunctivitis 3.9% in the gefitinib arm and 1.4% in the placebo arm. The frequency of dry eye was also slightly higher in gefitinib treated patients (1.4%) and (0.7%) in placebo treated patients. One SAE of toxic retinitis occurred in the gefitinib arm.

No evidence of any clinically relevant cardiac, renal, or hepatic toxicity, was reported in ISEL.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 38: Common (>2%) all cause adverse events occurring > 1.5 fold difference with gefitinib treatment (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 1126)		*Placebo (N = 562)*			
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*	*P-value**
Diarrhea	418	27.62	64	9.43	2.9	0.0
Rash	325	26.47	45	7.47	3.5	0.0
Dry skin	133	11.37	20	3.56	3.2	0.0
Pyrexia	93	7.46	32	4.8	1.6	0.0
Pruritus	85	7.19	29	4.63	1.6	0.0
Stomatitis	78	6.13	28	3.91	1.6	0.1
Conjunctivitis	54	4.09	11	1.6	2.6	0.0
Acne	45	4	7	0.89	4.5	0.0
Urinary tract infection	53	3.73	10	1.78	2.1	0.0
Abdominal pain	46	3.46	11	1.96	1.8	0.1
Paronychia	42	3.11	0	0	35.5	0.0
Weight decreased	35	3.11	10	1.78	1.7	0.1
Alopecia	27	2.31	9	1.42	1.6	0.3
Upper respiratory tract infection	28	2.13	7	1.25	1.7	0.3

* p-values are exploratory in nature; RR = relative risk

Reviewer Note: Common adverse events are in alignment with more significant adverse events, the major events being diarrhea, rash, and dry skin.

7.4.2 Laboratory Findings

Hematology:

Table 39: Hematologic laboratory evaluations and maximum grades reached regardless of baseline (Source: ISEL CSR and Dataset; Reviewer Table)

	Hematology: Maximum Grade Reached				
	Any Grade	1	2	3	4
Anemia					
Gefitinib (n=978)	81%	55%	23%	3%	0.5%
Placebo (n=493)	80%	53%	23%	4%	0.2%
Thrombocytopenia					
Gefitinib (n=978)	10.8%	9%	1%	0.8%	0
Placebo (n=492)	9%	8%	0.4%	1%	0
Neutropenia					
Gefitinib (n=963)	5%	3%	0.9%	0.4%	0.2%
Placebo (n=482)	6%	4%	1%	0.2%	0.6%

Reviewer Note: No significant differences in hematologic parameters occurred with gefitinib compared to placebo.

Chemistry and Hepatic:

Table 40: Significant chemistry and liver test abnormalities in ISEL (Source: ISEL CSR and Dataset; Reviewer Table)

	Chemistry: Maximum Grade Reached				
	Any Grade	1	2	3	4
Creatinine					
Gefitinib (n=973)	20%	16%	4%	0.2%	0
Placebo (n=489)	19%	16%	3%	0	0
ALT					
Gefitinib (n=967)	70%	62%	7%	2%	0.2%
Placebo (n=487)	23%	19%	3%	1%	0.2%
AST					
Gefitinib (n=954)	36%	28%	6%	2%	0.2%
Placebo (n=475)	25%	21%	3%	1%	0.2%
Alkaline phosphatase					
Gefitinib (n=963)	55%	44%	8%	3%	0
Placebo (n=485)	52%	43%	6%	3%	0.2%
Bilirubin					
Gefitinib (n=959)	8%	6%	1%	0.8%	0.1%
Placebo (n=485)	%	4%	2%	1%	0.6%

Reviewer Note: Gefitinib treated patients had a relatively high incidence of renal abnormalities, similar to other TKIs. In addition, compared to placebo, ALT increases were higher in gefitinib treated patients.

7.4.3 Vital Signs

Individual clinically significant changes from baseline in vital signs and physical examinations were reported as AEs. No clinically relevant trends in vital signs or physical examinations were observed that were related to trial medication

7.4.4 Electrocardiograms (ECGs)

Please see QTIRT review. In brief, based on other studies no significant change in QTcF interval was detected when single daily multiple doses of 250 mg gefitinib was administrated.

7.4.5 Special Safety Studies/Clinical Trials

n/a

7.4.6 Immunogenicity

n/a

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

None significant, please see clinical pharmacology review.

7.5.2 Time Dependency for Adverse Events

None significant.

7.5.3 Drug-Demographic Interactions

Table 41: Common adverse events occurring in males patients > 2% and 2 fold increase with gefitinib treatment (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 759)		*Placebo (N = 377)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*
Rash	207	25.3	29	6.9	3.7
Diarrhea	222	22.27	44	10.08	2.2
Dry skin	68	8.56	15	3.98	2.2
Acne	27	3.56	3	0.8	4.5
Conjunctivitis	27	3.03	5	1.33	2.3
Paronychia	22	2.37	0	0	18.4

Table 42: Common adverse events occurring in females patients > 2% and 2 fold increase with gefitinib treatment (Source: ISEL Dataset; Reviewer Table)

	Gefitinib (N = 367)		*Placebo (N = 185)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RR*
Rash	118	28.88	16	8.65	3.3
Diarrhea	196	38.69	20	8.11	4.8
Pruritus	47	11.99	13	5.41	2.2
Urinary tract infection	38	7.63	6	3.24	2.4
Dry skin	65	17.17	5	2.7	6.4
Conjunctivitis	27	6.27	6	2.16	2.9

Reviewer Note: Upon analysis of common adverse events in males and females, there appears to be no significant signal. Males do appear to have more paronychia and females urinary tract infections.

7.5.4 Drug-Disease Interactions

n/a

7.5.5 Drug-Drug Interactions

See clinical pharmacology review.

7.6 Additional Safety Evaluations

There have been many trials evaluating gefitinib monotherapy in different lines of therapy for NSCLC, both single arm studies and randomized studies. As mentioned above, a pooled analysis was conducted on the most relevant studies (ISEL, INTEREST, and IPASS) to determine the rare and significant adverse events. Important adverse events from pooled analysis relevant to the label are presented below.

Interstitial lung disease (ILD) encompassing the PTs of lung infiltration, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis, or abnormal chest X-ray occurred in 1.5% of the 2462 patients across clinical trials; of these, 0.8% were Grade 3 or higher and 3 cases were fatal.

Hepatotoxicity was seen across clinical trials. Approximately 11% of patients had increased alanine aminotransferase (ALT), 8% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin, Grade 3 or higher liver test abnormalities occurred in 5% (ALT), 3.0% (AST), and 0.7% (bilirubin). It is recommended to hold treatment for worsening liver function and discontinuation for severe hepatic impairment.

Diarrhea was a common toxicity associated with treatment and most cases were low grade. However, Grade 3 or 4 diarrhea occurred in 3% of 2462 patients across clinical trials.

Ocular disorders which included keratitis, conjunctivitis, blephritis, dry eye, corneal erosion, and aberrant eyelash growth occurred in 7% of the 2462 patients across clinical trials. The incidence of Grade 3 or 4 ocular disorders was 0.1% of which 2 cases were greater than Grade 3.
Common adverse events associated with gefitinib across these trials are presented below:

Table 43: Common adverse events (≥5%) occurring in gefitinib treated patients across clinical trials ISEL, INTEREST, and IPASS (Source: NDA206995 Summary of Clinical Safety; Reviewer Table)

Preferred Term	*Gefitinib n = 2462*			
	All		Grade ≥ 3	
	n	%	n	%
Diarrhea	858	35	73	3.0
Rash	833	34	42	1.7
Decreased appetite	484	20	47	1.9
Nausea	439	18	14	0.6
Dry skin	384	16	0	0
Vomiting	339	14	18	0.7
Fatigue	268	11	37	1.5
Constipation	261	11	19	0.8
Dyspnea	251	10	97	3.9
Pruritus	251	10	8	0.3
Cough	240	10	9	0.4
Acne	208	8	3	0.1
Stomatitis	203	8	3	0.1
Pyrexia	202	8	11	0.4
Insomnia	160	7	0	0
Asthenia	140	6	30	1.2
Headache	137	6	10	0.4
Paronychia	128	5	3	0.1
Dizziness	127	5	11	0.4
Nasopharyngitis	126	5	0	0
Anemia	124	5	32	1.3
Back pain	124	5	17	0.7

Reviewer Note: Upon analysis of adverse events across clinical trials, no new safety signal appears.

7.6.1 Human Carcinogenicity

Gefitinib has been tested for genotoxicity in a series of in vitro (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an in vivo rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage. Please see CMC review for full description.

7.6.2 Human Reproduction and Pregnancy Data

Gefitinib can cause fetal harm when administered to a pregnant woman. Studies in animals have demonstrated reproductive toxicity. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with gefitinib. Please see CMC review for full description.

7.6.3 Pediatrics and Assessment of Effects on Growth

Gefitinib has not been adequately studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no specific treatment in the event of overdose of gefitinib. A limited number of patients were treated with daily doses of up to 1000 mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhea and skin rash.

7.7 Additional Submissions / Safety Issues

Discussed above.

8 Postmarket Experience

Other than that which has already been described in this review, there are no important postmarket safety signals of concern.

To detect any additional safety signals, exposure to gefitinib was evaluated through the Oracle FDA Empirica Signal software. A search was conducted on the term “gefitinib” based on MedDRA PT AE terms. Search results were limited based on

1. Occurrence in more than 9 patients
2. An Empirical Bayesian Geometric Mean (EBGM) risk score of greater than 2 fold (EBGM is more stable estimate than relative risk).

Most of the signals observed have already been detected based on clinical trials. Strong major signals include diarrhea and pneumonia. The signal for ILD appears to be stronger than reported in trials.

Table 44: Empirica Analysis on gefitinib; AE signals occurring in >9 and EBGM score >2 fold (Source: EMPIRICA Signal; Reviewer Table)

Preferred Term	SOC	N	EBGM
Diarrhoea	**Gastr**	**506**	**4.12**
Interstitial lung disease	**Resp**	**317**	**14.9**
Rash	**Skin**	**311**	**3.68**
Pneumonia	**Infec**	**251**	**3.12**
Disease progression	**Genrl**	**197**	**6.24**
Hepatic function abnormal	**Hepat**	**172**	**8.88**
Neoplasm malignant	**Neopl**	**172**	**5.16**
Decreased appetite	**Metab**	**169**	**2.38**
Lung disorder	**Resp**	**157**	**10.7**
Dehydration	**Metab**	**143**	**2.53**
Respiratory failure	**Resp**	**129**	**3.3**
Pleural effusion	**Resp**	**113**	**4.02**
Alanine aminotransferase increased	**Inv**	**109**	**2.34**
Cough	**Resp**	**108**	**2.11**
Aspartate aminotransferase increased	**Inv**	**103**	**2.22**
Dry skin	**Skin**	**102**	**13.5**
Liver disorder	**Hepat**	**94**	**4.95**
Pulmonary embolism	**Resp**	**71**	**2.05**
Haemoptysis	**Resp**	**70**	**6.84**
Hypoxia	**Resp**	**67**	**3.75**
Stomatitis	**Gastr**	**63**	**5.26**
General physical health deterioration	**Genrl**	**62**	**2.08**
Alopecia	**Skin**	**59**	**2.78**
Acne	**Skin**	**56**	**17**
Metastases to central nervous system	**Neopl**	**56**	**15.5**
Lung neoplasm malignant	**Neopl**	**53**	**6.19**
Pneumonitis	**Resp**	**53**	**5.63**
Non-small cell lung cancer	**Neopl**	**50**	**25.4**
Pneumothorax	**Resp**	**45**	**4.97**
Lung infiltration	**Resp**	**43**	**4.29**
Blood lactate dehydrogenase increased	**Inv**	**41**	**2.3**
Dermatitis acneiform	**Skin**	**40**	**23.3**
Febrile neutropenia	**Blood**	**39**	**2.22**
Disseminated intravascular coagulation	**Blood**	**38**	**2.94**
Hypophagia	**Metab**	**38**	**2.75**
Mucosal inflammation	**Genrl**	**37**	**4.09**
Lymphangiosis carcinomatosa	**Neopl**	**34**	**30.3**
Cystitis haemorrhagic	**Renal**	**32**	**26.2**
Skin disorder	**Skin**	**32**	**4.63**
Haematuria	**Renal**	**32**	**2.25**
Pneumonia bacterial	**Infec**	**31**	**10.1**
Paronychia	**Infec**	**30**	**41.6**

Nail disorder	**Skin**	**28**	**13.3**
Acute respiratory failure	**Resp**	**28**	**4.7**
Metastases to liver	**Neopl**	**28**	**4.52**
Chest X-ray abnormal	**Inv**	**27**	**5.7**
Acute respiratory distress syndrome	**Resp**	**27**	**2.6**
Skin ulcer	**Skin**	**26**	**3.22**
Metastases to lung	**Neopl**	**25**	**6.09**
Pulmonary fibrosis	**Resp**	**25**	**2.88**
Pneumonia aspiration	**Resp**	**25**	**2.35**
Metastases to bone	**Neopl**	**24**	**5.39**
Productive cough	**Resp**	**24**	**2.99**
Oesophagitis	**Gastr**	**23**	**3.19**
Pericardial effusion	**Card**	**23**	**2.74**
Dyspnoea exertional	**Resp**	**23**	**2.22**
Performance status decreased	**Genrl**	**22**	**7.75**
Atelectasis	**Resp**	**22**	**2.49**
Pneumocystis jirovecii pneumonia	**Infec**	**21**	**3.97**
Dermatitis exfoliative	**Skin**	**20**	**3.04**
Herpes zoster	**Infec**	**20**	**2.03**
Skin toxicity	**Skin**	**19**	**24.1**
Neoplasm progression	**Neopl**	**19**	**4.51**
Radiation pneumonitis	**Inj&P**	**17**	**23.1**
Leukoencephalopathy	**Nerv**	**17**	**7.66**
Hepatotoxicity	**Hepat**	**17**	**2.32**
Dementia	**Nerv**	**17**	**2.28**
Pulmonary alveolar haemorrhage	**Resp**	**16**	**6.27**
Lung consolidation	**Resp**	**16**	**5.72**
Hypomagnesaemia	**Metab**	**16**	**3.86**
Lung infection	**Infec**	**16**	**2.72**
Ileus	**Gastr**	**16**	**2.59**
Folliculitis	**Infec**	**15**	**12**
Lung neoplasm	**Neopl**	**15**	**3.09**
Bronchopneumonia	**Infec**	**15**	**2.32**
Lung adenocarcinoma	**Neopl**	**14**	**8.68**
Palmar-plantar erythrodysasthesia syndrome	**Skin**	**14**	**3.26**
Hair growth abnormal	**Skin**	**13**	**6.2**
Metastasis	**Neopl**	**13**	**3.99**
Computerized tomogram abnormal	**Inv**	**13**	**3.74**
Dermatitis	**Skin**	**13**	**2.4**
Pulmonary haemorrhage	**Resp**	**13**	**2.05**
Skin fissures	**Skin**	**12**	**5.24**
PO2 decreased	**Inv**	**12**	**3.43**
Conjunctivitis	**Infec**	**12**	**2.37**
Lower respiratory tract infection	**Infec**	**12**	**2.07**
Metastases to adrenals	**Neopl**	**11**	**17**
Hair texture abnormal	**Skin**	**11**	**6.12**

Lung cancer metastatic	**Neopl**	**11**	**5.02**
Rash pustular	**Infec**	**11**	**2.79**
Lobar pneumonia	**Infec**	**11**	**2.56**
Metastases to meninges	**Neopl**	**10**	**13**
Traumatic lung injury	**Inj&P**	**10**	**5.12**
Skin infection	**Infec**	**10**	**3.49**

Figure 35: Top 25 Empirica signal association occurring in at least 10 and EBGM > 2 fold. (Source: EMPIRICA Signal; Reviewer Figure)

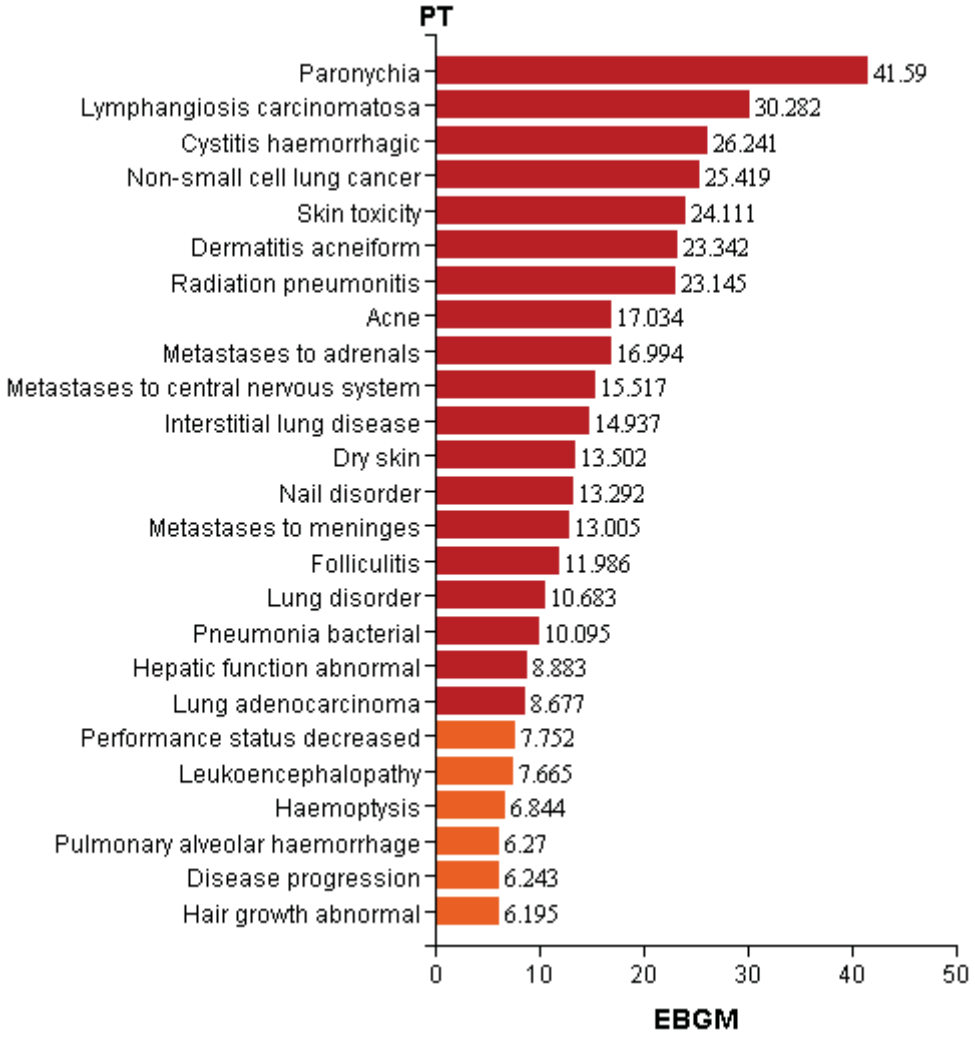
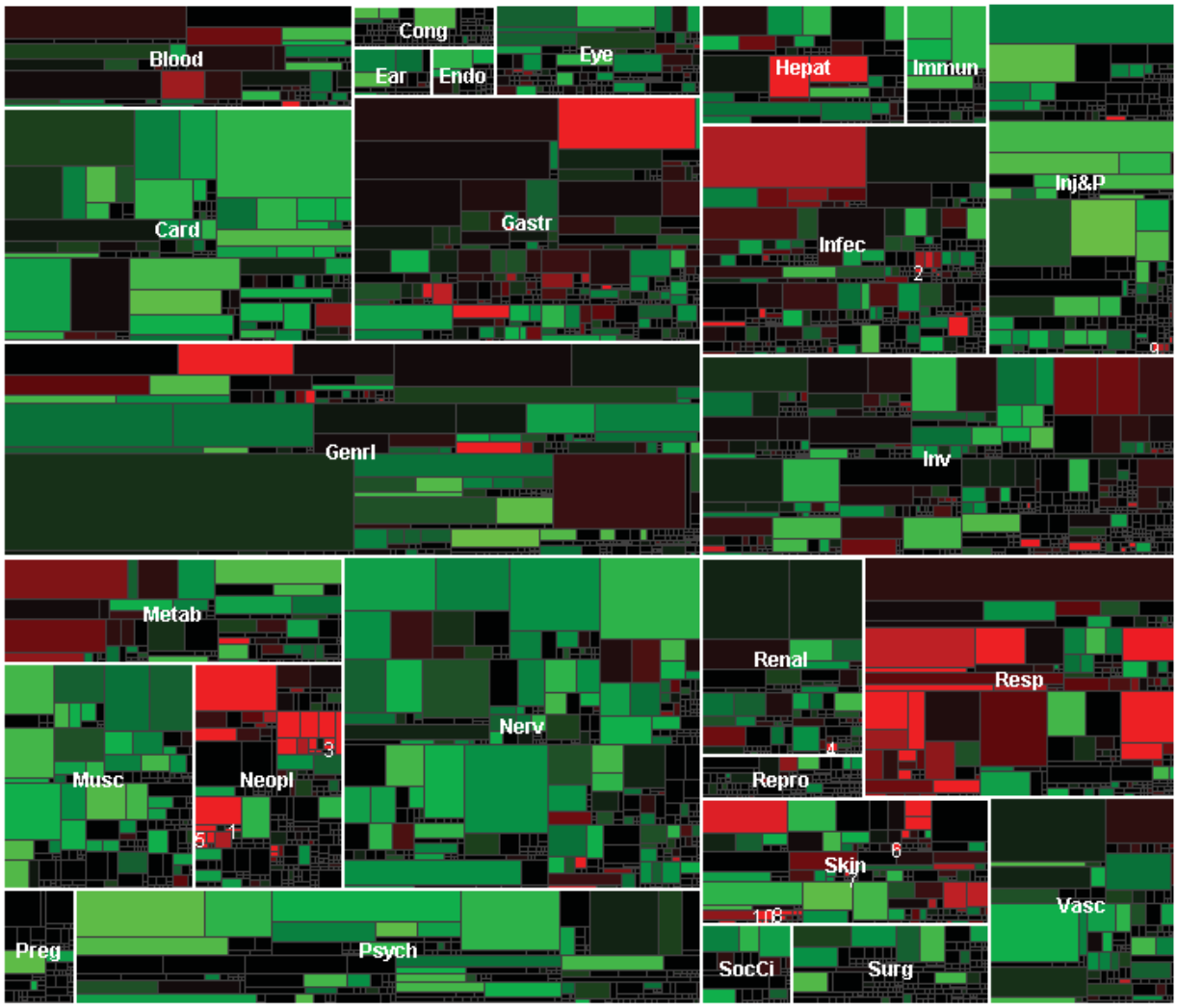


Figure 36: Heat Map of Adverse Events: Rank Order List Based on EBGM Risk (Source: EMPIRICA Signal; Reviewer Figure)



Rank	SOC	Term (PT)	EBGM
1	Neopl	Lung carcinoma cell type unspecified recurrent	49.791
2	Infec	Paronychia	41.590
3	Neopl	Lymphangiosis carcinomatosa	30.282
4	Renal	Cystitis haemorrhagic	26.241
5	Neopl	Non-small cell lung cancer	25.419
6	Skin	Skin toxicity	24.111
7	Skin	Eczema asteatotic	23.786
8	Skin	Dermatitis acneiform	23.342
9	Inj&P	Radiation pneumonitis	23.145
10	Skin	Acne	17.034

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following labeling recommendations were made:

1. The indication for gefitinib included [redacted] (b) (4) metastatic and the clinical review team recommended to remove [redacted] (b) (6) to make it more consistent with other product labels. Most patients had metastatic disease as per AJCC version 7 criteria.
2. The limitations of use section in the label was modified to add that safety and efficacy of gefitinib has not been established in patients with T790M or exon 20 insertion mutation NSCLC.
3. Warnings and precautions was modified [redacted] (b) (4)
4. Description of clinical studies was modified to only include details pertinent to the safety or efficacy assessment.
5. Common laboratory abnormalities table was modified to include maximum grade toxicity and not only shifts.
6. Table 3 was modified to move the BICR assessment to the middle column given its regulatory importance.

9.3 Advisory Committee Meeting

The NDA was not presented to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant efficacy or safety issues for the proposed indication, and outside expertise from ODAC was not considered necessary since there were no controversial issues that would benefit from advisory committee discussion.

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/s/

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05/28/2015

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05/29/2015