CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

The applicant submitted data and final study report of a single arm study to support approval for gefitinib as the treatment of patients with (b) (4) metastatic non-small-cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test. Gefitinib had initially received accelerated approval in 2003 but was subsequently voluntarily withdrawn.

This application was based on a single arm study, the IFUM study (D791AC00014) study, 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)." The primary endpoint was objective response rate (ORR) per the RECIST 1.1 criteria. The study planned to enroll 100 patients.

A total of 106 patients were included in the final analysis. The ORR assessed by the investigators was 69.8% with 95% confidence interval (CI): (60.5%, 77.7%), and the corresponding median duration of response was 8.3 months with 95% CI: (7.6, 11.3). The ORR assessed by the independent review was 50% with 95% CI: (40.6%, 59.4%), and the corresponding median duration of response was 6.0 months with 95% CI: (5.6, 11.1).

A retrospective subgroup analysis of the IPASS study (D791AC00007) was also submitted to support the application. The IPASS study was titled "An Open Label, Randomised, Parallel Group, Multicentre, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib (IRESSA™) (250mg tablet) 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". The study enrolled 1217 patients. A total of 261 patients with evaluable tumor samples were EGFR mutation positive by the same clinical trial assay used in the IFUM study. Of these 261 patients, 186 (71%) had radiographic scans available for assessment by a blinded independent central review (BICR). The retrospective analysis of these 186 patients suggested gefitinib prolonged improvement with respect to progression free survival (PFS) compared to carboplatin/paclitaxel.

Based on the data and analyses, the results showed 50% ORR in gefitinib treated patients. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

2. INTRODUCTION

The applicant submitted data and final study report of a pivotal study to seek regular approval for a new indication for gefitinib. This application was based on the IFUM study (D791AC00014), an open-label, multicenter, single-arm study of gefitinib 250 mg as first-line treatment in Caucasian patients with epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). A retrospective subgroup analysis of the IPASS study (D791AC00007) was also submitted to support the application. The IPASS study was an open label, randomized, phase III study of gefitinib versus carboplatin/paclitaxel doublet chemotherapy in patients with advanced NSCLC in Asia.

2.1 Overview

2.1.1. Class and Indication

Gefitinib is an Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor designed to target signaling through the EGFR pathway, and is designed to offer an alternative to chemotherapy. The applicant is seeking indication for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Another kinase inhibitor, erlotinib, was approved for the same indication: first-line treatment for NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test). The approval was based on a randomized, open-label study conducted in Europe. A total of 174 Caucasian patients were randomized 1:1 to either erlotinib or standard platinum-based doublet chemotherapy. Erlotinib showed a statistically significant improvement in progression free survival (PFS) with a hazard ratio (HR) of 0.34 (95% CI: 0.23, 0.49). The median PFS was 10.4 months in the erlotinib arm and 5.2 months in the chemotherapy arm. Erlotinib did not show statistically significant improvement in overall survival (OS) at time of the PFS analysis. The objective response rate was 65% in the erlotinib arm and 16% in the chemotherapy arm.

2.1.2. Regulatory History

Gefitinib had initially received accelerated approval in 2003 but was subsequently voluntarily withdrawn. Several randomized studies had failed to demonstrate efficacy of gefitinib in an unselected population. Since then, it became clear that patients who are most likely to benefit from gefitinib are those with drug-sensitive activating mutations in EGFR.

Gefitinib received accelerated approval for 3rd line advanced NSCLC in May 2003. AstraZeneca initiated 3 confirmatory randomized Phase 3 studies as US post-approval

commitment studies, which were Study IBREESE (D7913C00710), Study ISEL (D7913C00709), and Study INTEREST (D791GC0001). These studies failed to verify and confirm clinical benefit. In June 2005, FDA withdrew approval for new patients and the use of gefitinib was restricted to those who were already benefiting from it. In September 2011, the NDA approval was voluntarily withdrawn by the applicant.

In March 2014, FDA and the applicant held a Pre-NDA meeting to discuss new indication for patients with advanced NSCLC where the tumor was EGFR mutation positive. The NDA was submitted in on September 17, 2014.

2.1.3. Study Reviewed

The sponsor has resubmitted gefitinib for US approval. In regard to this review, the IFUM study is considered pivotal and the IPASS as supportive for efficacy.

IFUM

The IFUM study was an open-label, multicenter, single arm study to assess efficacy, safety and tolerability of gefitinib as first line treatment in Caucasian patients, who have EGFR mutation positive locally advanced or metastatic NSCLC.

Eligible patients with EGFR mutation positive NSCLC received gefitinib treatment 250 mg orally once daily. The primary objective of this study was to evaluate objective response rate (ORR) per RECIST1.1 criteria by the investigator. ORR by central review was also reported. Secondary endpoints included disease control rate (DCR), progression free survival (PFS) and overall survival (OS).

A total of 1060 patients were screened and 107 were included in the final analysis set. The first patient was enrolled on September 8, 2010, the last patient was enrolled on February 15, 2012, and the data cut-off date was August 15, 2012.

IPASS

The IPASS Study was a Phase 3, randomized, open-label, parallel group, multi-center study to assess efficacy, safety and tolerability of gefitinib versus carboplatin / paclitaxel doublet chemotherapy as first-line treatment in patients with advanced (Stage IIIB or IV) NSCLC in Asia.

Patients were randomized in a 1:1 ratio to receive either gefitinib or carboplatin and paclitaxel doublet chemotherapy. The primary objective of this study was to test for non-inferiority in progression free survival (PFS) of patients treated by gefitinib versus carboplatin / paclitaxel. The secondary objective was to test superiority in PFS. Overall survival (OS) would be analyzed in the same manner.

A total of 1217 patients were randomized in a 1:1 allocation with 609 in the gefitinib arm and 608 in the carboplatin / paclitaxel arm. The study was initiated on March 29, 2006 and the data cut-off date was April 14, 2008.

This review will focus on the subgroup of patients with EGFR mutation positive tumor.

2.2 Data Sources

Data used for review is from the electronic submission received on June 30, 2014. The network path is

- \\CDSESUB1\evsprod\NDA206995\206995.enx .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

IFUM

The IFUM study was an open-label, multicenter, single arm study to assess efficacy, safety and tolerability of gefitinib as first line treatment in Caucasian patients, who have EGFR mutation positive locally advanced or metastatic NSCLC.

Patients needed to have measurable disease according to the RECIST 1.1 criteria and World Health Organization (WHO) performance status 0-2, and were selected for open label gefitinib treatment on the basis of EGFR mutation positive status of their tumor sample at enrollment, regardless of their clinical characteristics. Eligible patients with EGFR mutation positive NSCLC received gefitinib treatment 250 mg orally once daily. From the start of study, patients visits were scheduled every 3 weeks until Visit 6 (week 12), and every 6 weeks from Visit 6 (week 12) as long as they were receiving study treatment. Baseline radiological assessment using RECIST 1.1 were performed at screening and every 6 weeks after the start of study until objective disease progression. Study treatment was given until objective disease progression was documented or other criterion for discontinuation was met. Patients who discontinued gefitinib treatment for reasons other than objective disease progression would continue to undergo RECIST 1.1 tumor assessments every 6 weeks until objective disease progression. Upon documentation of objective disease progression, all patients would enter survival follow up. Survival information was collected every 8 weeks until death, withdrawal of consent, loss to follow-up or end of study.

The primary objective of this study was to evaluate objective response rate (ORR) per RECIST1.1 criteria by the investigator. ORR by central review was also reported. Secondary endpoints included disease control rate (DCR), progression free survival (PFS) and overall survival (OS).

Reviewer's Comment:

The time-to-event endpoints, PFS and OS, are not interpretable in single-arm trials, and therefore are considered as exploratory. DCR should not be included in the label as this measurement includes the natural course of disease. .

IPASS

The IPASS study was a Phase 3, randomized, open-label, parallel group, multi-center study to assess the effect of gefitinib 250 mg tablet orally per day on PFS in patients with advanced NSCLC in Asia.

Patients were randomized in a 1:1 ratio to receive either gefitinib or carboplatin and paclitaxel doublet chemotherapy. Randomization was stratified by performance status (0-1 vs. 2), smoking history (never vs. light ex-smoker), and gender (male vs. female). Gefitinib 250 mg tablet was administered orally per day until progression or other discontinuation criteria were met. In the control arm carboplatin AUC 5.0 or 6.0 and paclitaxel 200 mg/m^2 on day 1 every 3 weeks was administered for a maximum of 6 cycles. Patients progressing on the gefitinib arm were to receive carboplatin / paclitaxel doublet chemotherapy as second line study treatment for a maximum of 6 cycles.

The primary objective of this study was to test for non-inferiority in progression free survival (PFS) of patients treated by gefitinib versus carboplatin / paclitaxel. The secondary objective was to test superiority in PFS. Secondary endpoints included OS and objective response rate (ORR). Subgroup analysis based on biomarker status was one of the exploratory analyses.

An interim analysis was planned at 150 PFS events for futility only.

Reviewer's Comments:

A subgroup analysis of IPASS based on EGFR mutation status is considered as supportive evidence for this NDA.

3.2.2. Efficacy Measures

IFUM

The primary endpoint ORR was defined as the percentage of EGFR mutation positive patients who have a confirmed complete response [CR] or partial response [PR] before any evidence of progression as defined by RECIST 1.1. A confirmed response of CR or PR means that a response of CR or PR is recorded at a visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits. The ORR by study investigator was the primary outcome and ORR by central review was supportive.

Reviewer's Comments:

It is recommended to use the ORR determinations by independent review as the primary ORR outcome rather than those by investigator assessment because the investigators may introduce bias in assessment in a single-arm, open-label clinical study.

IPASS

The primary endpoint PFS was defined as the time from randomization to the first documentation of objective disease progression (PD) or death from any cause. Secondary endpoint included OS and ORR.

3.2.3. Sample Size Consideration

IFUM

In the final IFUM study protocol, a total of 100 patients were expected to be enrolled into the study after screening 1250 Caucasian patients.

Reviewer's Comments:

The protocol did not provide power analysis for the sample size calculation. The sample size was arbitrarily chosen.

IPASS

The IPASS Study's primary objective was to demonstrate non-inferiority of gefitinib compared with chemotherapy. The sample size consideration was based on the following estimates and assumptions:

- 1:1 randomization scheme.
- Two-sided type I error rate of 0.05 and 80% power.
- The non-inferiority margin for PFS was a hazard ratio (HR) of 1.2.
- The PFS in the carboplatin/paclitaxel arm was 6 months.

The planned sample size was 1212 patients with 944 PFS events for the final analysis. A total of 1217 patients were randomized with 609 in the gefitinib arm and 608 in the carboplatin / paclitaxel arm. The patients would then continue to be followed for survival until 944 deaths occurred.

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Reviewer's Comments:

An exploratory analysis was proposed to collect optimal tumors samples for biomarker analysis to investigate baseline biomarker data to ascertain if there are any biomarkers that differentiate for a relative treatment effect when comparing gefitinib to carboplatin /paclitaxel doublet chemotherapy. The number of patients who would agree to participate in this optional research was unknown at the time of the study.

3.2.4. Statistical Methodologies

IFUM

The full analysis set (FAS) was used for the primary efficacy analysis. FAS comprises of all patients who were found to be EGFR mutation positive and entered into the study.

The ORR will be calculated as the percentage of FAS patients who have a confirmed CR or PR before any evidence of progression (as defined by RECIST 1.1). A 95% confidence interval (CI) was derived for the ORR using Wilson score intervals as follows:

$$CI = \frac{2np + z^2 + 4npq}{2\,(n + z^2)}$$

where n = number of patients, p = ORR, q = 1-p and z = Normal probability statistic (1.960 for 95% CI).

Reviewer's Comments:

The protocol also provided analysis methods for DCR, PFS and OS, which were considered as exploratory analyses.

IPASS

The Intent-to-Treat (ITT) population was used for the efficacy analysis. The ITT population comprises of all randomized patients regardless of whether or not treatment was administered.

The primary statistical analysis comparing PFS between gefitinib and carboplatin / paclitaxel used a stratified proportional hazards model. The null hypothesis of survival inferiority would be rejected and non-inferiority would be concluded if the upper 95% confidence limit was below 1.2. If the null hypothesis of inferiority is rejected and if the upper 95% confidence limit for the hazard ratio was below 1.0 then superior PFS for gefitinib would be declared. PFS will also be displayed graphically using Kaplan-Meier plots. OS would be analyzed using the same procedure as that of PFS.

Reviewer's Comments:

The margin for non-inferiority was a fixed margin, arbitrarily selected by the applicant.

The protocol also specified several exploratory biomarker analyses and EGFR was one of them. It was planned to examine the tissue samples collected for evaluation of EGFR protein expression. The outcome of this analysis might determine a set of biomarkers to enable patient selection for treatment with gefitinib.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

IFUM

A total of 1060 patients were screened and 106 were included in the final analysis set. The first patient was enrolled on September 8, 2010, the last patient was enrolled on February 15, 2012, and the data cut-off date was August 15, 2012.

A total of 1060 Caucasian patients with locally advanced or metastatic NSCLC were screened, of whom 118 patients were EGFR mutation positive. Of these 118 patients, 12 patients did not received treatment due to death, consent withdrawal, eligibility criteria, adverse events, or non-compliance. There were 107 patients received gefitinib, and one patient was ineligible due to Exon 20 mutation. The final FAS contained 106 patients. The disposition of the FAS patients are presented in the following table.

Table 1. IFUM Patient Disposition

Disposition	N (%)
Patients in FAS	106 (100)
Patients Discontinued Treatment	57 (54)
Adverse Event	6 (6)
Disease Progression	44 (42)
Other	7 (7)
Patients Discontinued Study	35 (33)
Death	29 (27)
Other	1 (1)
Patient Decision	3 (3)
Lost to Follow-up	2 (2)
Patient Ongoing Study	71 (67)

Demographic data at baseline are summarized in the following table.

Table 2. IFUM Patients Demographics

Demographics	N (%)
Patients in FAS	106 (100)
Age	
<= 65	55 (52)
> 65	51 (48)
Sex	
Male	31 (29)
Female	75 (71)
Race	
White	106 (100)
Other	0

Disease characteristics at baseline are summarized in the following table.

Table 3. IFUM Patients Baseline Characteristics

Baseline Characteristics	N (%)
Patients in FAS	106 (100)
ECOG Status	
0	48 (45)
1	51 (48)
2	7 (7)
Histology Type	
Adenocarcinoma	103 (97)
Non-Adenocarcinoma	3 (3)
Smoking Status	
Current	6 (6)
Former	32 (31)
Never	68 (64)
Disease Stage	
Locally Advanced	8 (8)
Metastatic	98 (92)
Time from Original Diagnosis to Enrollment	
>=6 Months	34 (32)
< 6 Months	55 (52)
Unknown	17 (16)

Reviewer's comments:

The demographic and baseline characteristics are from the 106 patients in the FAS population. All subjects were Caucasians. About 30% of the patients were males. Most of the patients had adenocarcinoma. Most patients had metastatic disease. Most patients were currently non-smokers with 68% who were never-smokers.

IPASS

A total of 1217 patients were randomized in a 1:1 allocation with 609 in the gefitinib arm and 608 in the carboplatin / paclitaxel arm. The study was initiated on March 29, 2006 and the data cut-off date was April 14.

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 central review.

The demographic and baseline characteristics of the EGFR mutation positive patients are summarized in the following table.

Table 4. IPASS Demographic and Baseline Characteristics of EGFR Positive Patients

	Gefitinib N (%)	**Carboplatin / Paclitaxel** N (%)
Total	132 (100)	129 (100)
Gender		
Male	24 (18)	26 (20)
Female	108 (82)	103 (80)
Race		
Caucasian	1 (1)	0
Oriental	129 (98)	129 (100)
Other	2 (2)	0
Age		
< 65	95 (72)	90 (70)
≥ 65	37 (28)	39 (30)
Smoking Status		
Ex-smoker	124 (94)	122 (95)
Smoker	8 (6)	7 (5)
WHO Performance Status		
0	30 (23)	39 (30)
1	89 (67)	83 (64)
2	13 (10)	7 (5)
Disease Stage at Screening		
Locally Advanced	19 (14)	29 (22)
Metastatic	113 (86)	100 (78)

Reviewer's comments:

While all patients in the IFUM study were Caucasians, almost all patients in this group were Asians. The majority of the patients were females. More than two thirds of the patients were younger than 65 years. Most patients had metastatic disease. More than 90% of the patients were currently non-smokers.

3.2.6. Results and Conclusions

IFUM

Based on the 106 patients in the FAS population, there were a total of 74 responders per investigator's assessment, and 53 responders per central review. The following table summarizes the ORR results.

Table 5. IFUM ORR Analysis Results

	N (%)	95 % CI
Patients in FAS	106 (100)	
ORR by Investigator		
CR+PR (%)	74 (69.8)	(60.5, 77.7)
CR	2 (1.9)	
PR	72 (67.9)	
SD	22 (20.8)	
PD	10 (9.4)	
ORR by Central Review		
CR+PR (%)	53 (50.0)	(40.6, 59.4)
CR	1 (0.9)	
PR	52 (49.1)	
SD	41 (38.7)	
PD	12 (11.3)	

The results for duration of responses are presented in the following table.

Table 6. IFUM Duration of Response Results

	Median (Months)	**95% CI**
Investigator	8.3	(7.6, 11.3)
Central Review	6	(5.6, 11.1)

Reviewer's comments:

The investigator and central review's results had 65% agreement rate in response. The study was supposed to enroll patients with measurable disease. There were 17 patients without measurable disease at baseline. For 16 of these 17 patients, the central review considered multiple lung nodules as non-target lesions. As a post-hoc analysis, if these 17 patients were excluded then the ORR by central review would be about 60%.

IPASS

There were 261 patients with positive EGFR mutation in the ITT population, with 132 in the gefitinib arm and 129 in the carboplatin / paclitaxel arm. A total of 92 patients

progressed or died at time of the primary analysis, of which 32 were in the gefitinib arm and 60 in the placebo arm.

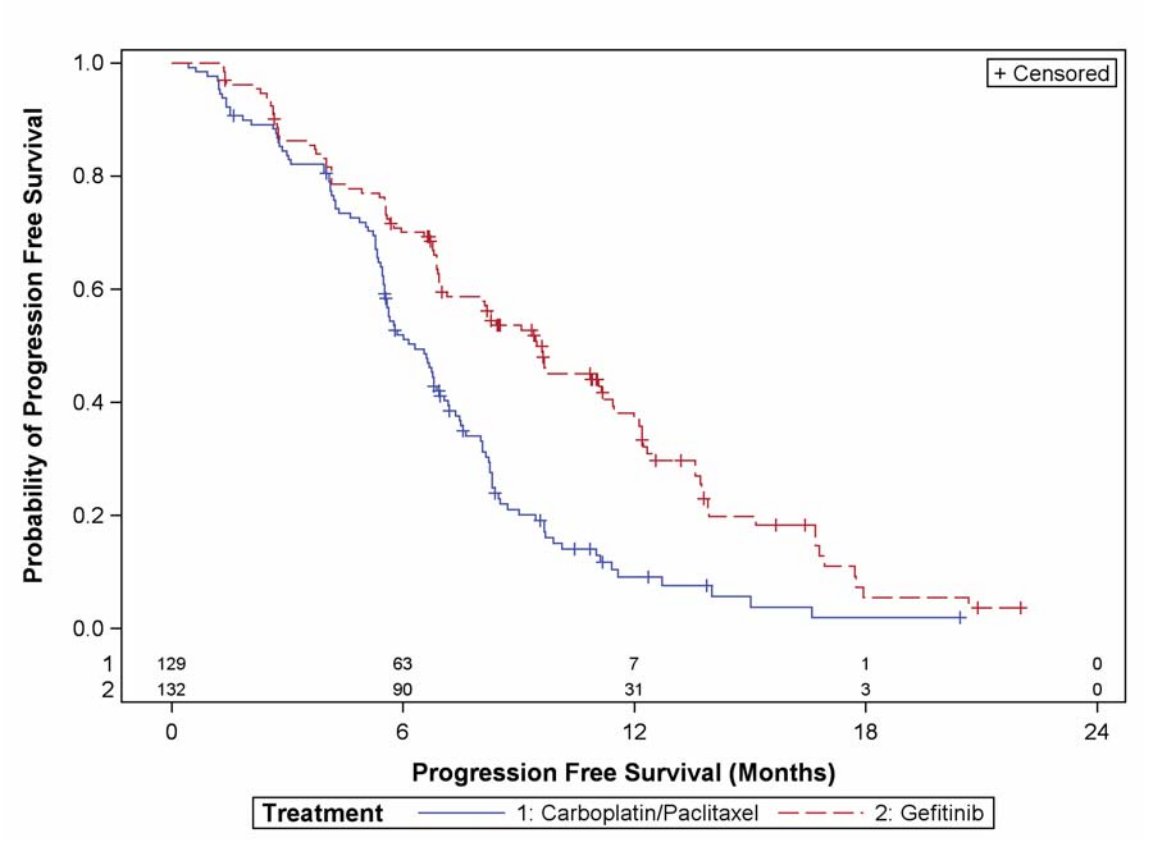
The following table summarizes the main analysis results of the PFS in the patients with positive EGFR mutation. Gefitinib was shown prolonging PFS to carboplatin / paclitaxel based on a stratified log-rank test stratified by WHO performance status, smoking status and sex. The median PFS was 9.5 months in the gefitinib arm and 6.3 months in the carboplatin / paclitaxel arm. The estimated HR was 0.48 with 95% CI (0.36, 0.64) based on a Cox model stratified by progression at baseline and previous therapy at entry.

Table 7. IPASS PFS in EGFR Positive Subgroup

	Gefitinib N = 132	**Carboplatin / Paclitaxel** N = 129
Number of Events (%)	97 (73.5%)	111 (86.0%)
Median PFS (95% CI)	9.5 (7.1, 11.2)	6.3 (5.6, 7.0)
HR (95% CI)	0.48 (0.36, 0.64)	

The following figure shows the estimated Kaplan-Meier curves for the distribution of PFS.

Figure 1. IPASS K-M Curves of PFS in EGFR Positive Subgroup



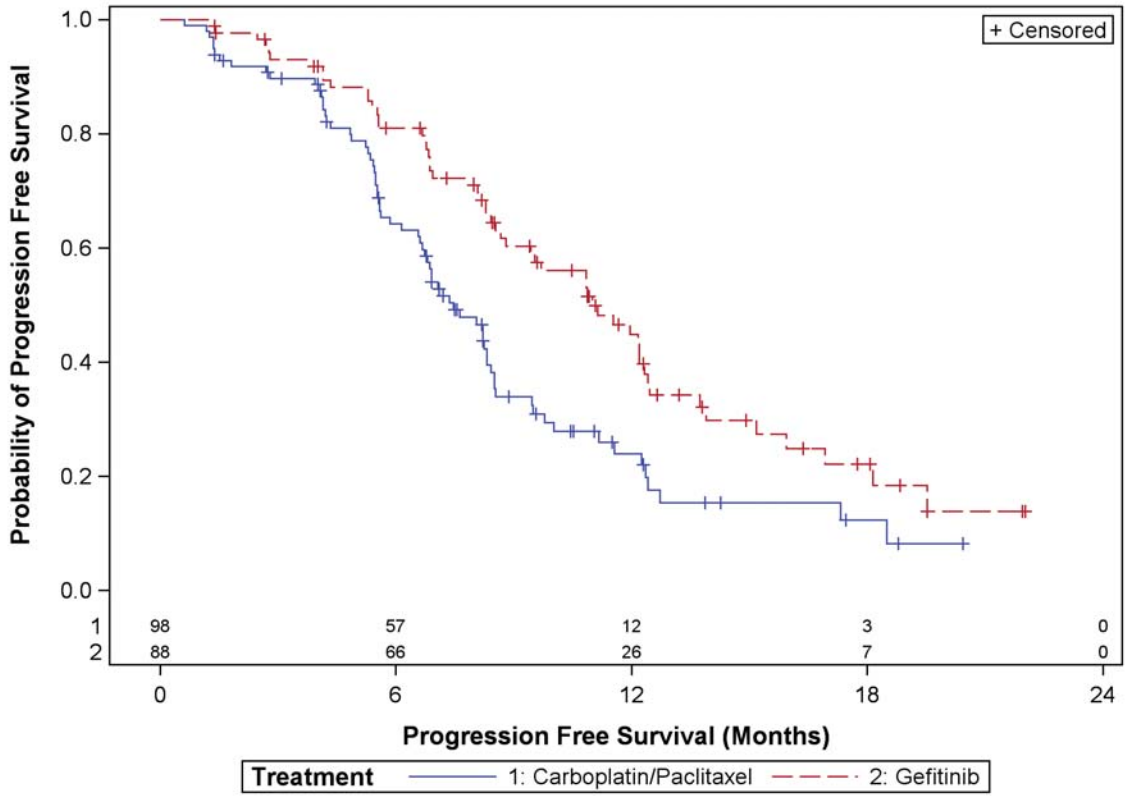
Among the 216 patients, central review of PFS events was performed for 186 of them. The following table summarizes the main results by central review.

Table 8. IPASS PFS in EGFR Positive Subgroup by Central Review

	Gefitinib N = 88	**Carboplatin / Paclitaxel** N = 98
Number of Events (%)	55 (62.5%)	69 (70.4%)
Median PFS (95% CI)	11.0 (8.8, 12.3)	7.5 (6.7, 8.3)
HR (95% CI)	0.55 (0.38, 0.79)	

The following figure shows the estimated Kaplan-Meier curves for the distribution of PFS by central review.

Figure 2. IPASS K-M Curves of PFS in EGFR Positive Subgroup by Central Review



Reviewer's comments:

These analyses are all retrospective and considered as supportive evidence for the application.

The results by investigator and central review did not show any important difference and are consistent to each other.

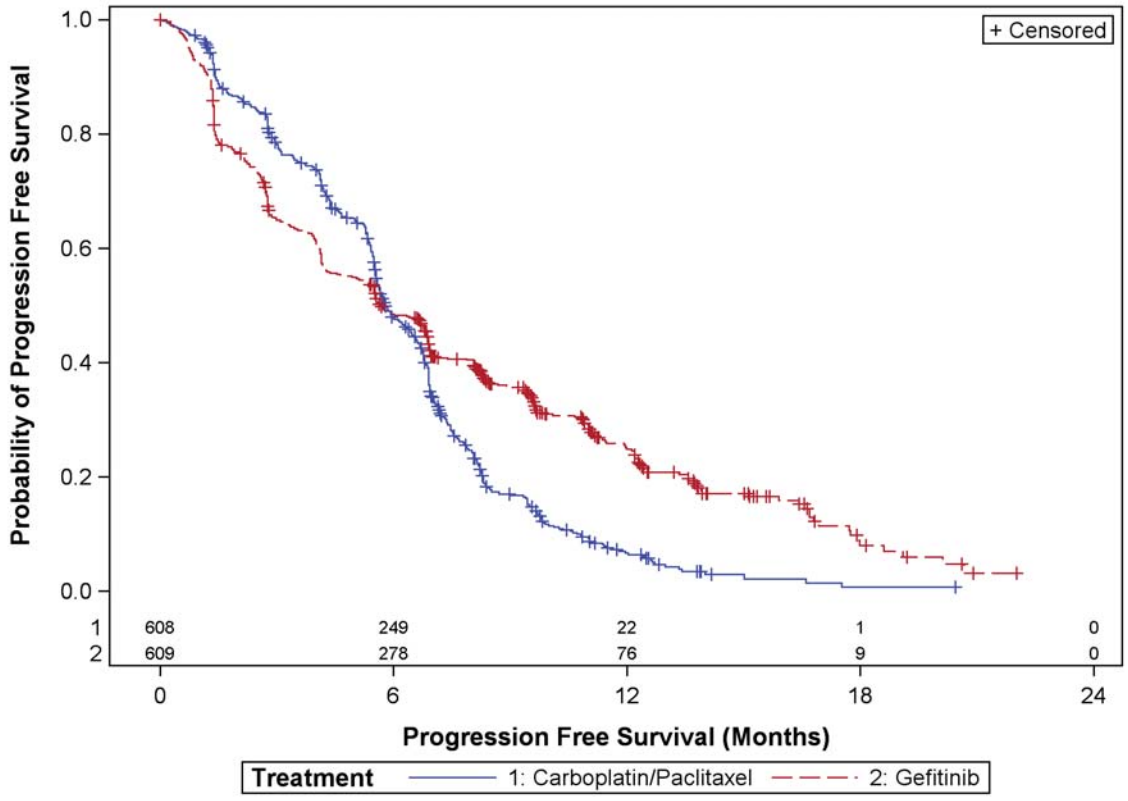
The results of the ITT populations are summarized in the following table. There were a total of 1217 patients in the ITT population in the IPASS study.

Table 9. IPASS PFS Results in ITT Population

	Gefitinib	Carboplatin / Paclitaxel
	N = 609	N = 608
Number of Events (%)	453 (74.4%)	497 (81.7%)
Median PFS (95% CI)	5.7 (5.4, 6.8)	5.8 (5.6, 6.4)
HR (95% CI)	0.74 (0.65, 0.85)	
p-value	<0.0001	

The following figure shows the estimated Kaplan-Meier curves for the distribution of PFS.

Figure 3. IPASS K-M Curves of PFS in ITT Population



While the applicant claimed the study was a success based on the HR of PFS, the median survival of the two treatment arms were almost the same. The Kaplan-Meier curves were crossed near the median. This is an indication that there were two subgroups performing differently in the ITT population. Gefitinib had a negative effect among patients with EGFR mutation negative tumor.

The study also failed to show improvement in OS in the ITT population. There were 223 deaths in the gefitinib arm and 227 deaths in the carboplatin / paclitaxel arm. Median survival was 18.6 months in the gefitinib arm and 17.3 months in the carboplatin / paclitaxel arm. The observed HR was 0.91 with 95% CI (0.76, 1.10).

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

IFUM

The following table summarizes the subgroup analysis of ORR based the FAS population. Race and region were not included because all the patients are Caucasians from Europe.

Table 10. IFUM ORR Subgroup Analysis

	Investigator		Central Review	
	n/N	ORR (95% CI)	n/N	ORR (95% CI)
Age				
≤ 65	36 / 55	65% (51%, 78%)	27 / 55	49% (35%, 63%)
> 65	38 / 51	75% (60%, 86%)	26 / 51	51% (37%, 65%)
Sex				
Male	22 / 31	71% (52%, 86%)	13 /31	48% (30%, 67%)
Female	52 / 75	69% (58%, 79%)	38 / 75	51% (39%, 62%)

Reviewer's comments:

The analyses showed that the ORR results for subgroups were consistent with the primary result.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The IFUM study included 106 patients in the final analysis. The ORR assessed by the investigators was 69.8% with 95% confidence interval (CI): (60.5%, 77.7%), and the corresponding median duration of response was 8.3 months with 95% CI: (7.6, 11.3). The ORR assessed by the independent review was 50% with 95% CI: (40.6%, 59.4%), and the corresponding median duration of response was 6.0 months with 95% CI: (5.6, 11.1).

A retrospective subgroup analysis of the IPASS study was considered as supportive evidence for the application. There were 261 patients with positive EGFR mutation in the ITT population, with 132 in the gefitinib arm and 129 in the carboplatin / paclitaxel arm. A total of 92 patients progressed or died at time of the primary analysis, of which 32 were in the gefitinib arm and 60 in the placebo arm. Patients in the gefitinib arm had longer PFS compared with those in the carboplatin / paclitaxel arm based on a stratified log-rank test stratified by WHO performance status, smoking status and sex. The median PFS was 9.5 months in the gefitinib arm and 6.3 months in the carboplatin / paclitaxel arm. The estimated HR was 0.48 with 95% CI (0.36, 0.64) based on a Cox model stratified by progression at baseline and previous therapy at entry. The analyses were not adjusted for multiplicity. The PFS results in the ITT population reported a statistically significant HR but did not show any improvement in median PFS, and the two Kaplan-Meier curves by two treatment arms are crossed around the median. The study also failed to show improvement in OS.

5.2 Conclusions and Recommendations

Based on the data and analyses, the results showed a 50% ORR in gefitinib treated patients. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

5.3 Labeling Recommendations

1. For the IFUM study, both ORR results by investigator and central review should be included in the label.
2. The PFS result of the retrospective subgroup analysis from IPASS is supportive but should not be described in detail in the label.

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/s/

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05/22/2015

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