Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Gefitinib

Proprietary Product Name: Iressa

Sponsor: AstraZeneca Pty Ltd

June 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension
Decision:	Approved
Date of Decision:	29 June 2010
Active ingredient(s):	Gefitinib
Product Name(s):	Iressa
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde 2113
Dose form(s):	Film-coated tablet
Strength(s):	250 mg
Container(s):	Blister pack
Pack size(s):	30
Approved Therapeutic use:	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase.
Route(s) of administration:	Oral
Dosage:	250 mg once daily
ARTG Number (s)	90010

Product background

Gefitinib is a selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (TK), commonly expressed in human solid tumours of epithelial origin. Inhibition of EGFR tyrosine kinase inhibits tumour growth and metastasis.

Following oral administration, gefitinib is slowly absorbed (time to maximal plasma concentration [T_{max}] 3-7 hours), extensively metabolised and slowly eliminated (mean half-life ($t_{½}$) 41 hours). Mean absolute bioavailability is 59% in cancer patients. Gastrointestinal and dermatological adverse effects are common. Serious effects are interstitial lung disease (ILD) and hepatitis.

The Australian Drug Evaluation Committee (ADEC) recommended rejection of an application for an extension of indications for pre-treated patients (based on the INTEREST study) in June 2009. After considering the ADEC advice and sponsor's response, the Delegate proposed rejection on the grounds that the efficacy of Iressa was not sufficiently well characterized to define an appropriate indication and, in particular, the

indication needs to take into account the results of the IPASS trial which suggest that EGFR mutation status may be a predictor of response to Iressa.

The sponsor, AstraZeneca Pty Ltd, has now re-submitted an application consisting of the original INTEREST data together with the IPASS study, in order to support an indication for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have activating mutations of the EGFR TK (which incorporates the results of the IPASS trial) as well as for the original extension of indications for pre-treated patients.

The proposed first line indication is:

For the first-line treatment of patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) who have activating mutations of the EGFR TK.

The existing pre-treated indication was for:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously failed chemotherapy and who have never smoked or have already been taking gefitinib and have demonstrated some benefit.

In addition, the sponsor applied to modify this indication as follows:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), who have previously ~~failed~~ received chemotherapy and ~~who have never smoked or have already been taking gefitinib and have demonstrated some benefit~~ are eligible for further chemotherapy.

Tarceva (erlotinib) is a similar product registered for second line use in non-small cell lung cancer (NSCLC) as follows:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

Regulatory status

Gefitinib was approved in patients with an activating EGFR mutation of a TKI in the European Union (EU) on 24 June 2009. The approved indication is as follows:

Iressa is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 5.1).

The IPASS trial was incorporated as supplementary data to an earlier pivotal trial (INTEREST) for patients who had received prior chemotherapy.

The application was also approved in Canada in December 2009 with the following indication:

Iressa (gefitinib) is indicated for the first line treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have activating mutations of the EGFR-TK.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Quality summary and conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical findings

Nonclinical summary and conclusions

There was no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical findings

Introduction

The pivotal study presented in this submission was the IPASS trial, which is a randomised open label parallel group Phase III study involving 87 centres in Asia. The primary objective of the trial was to compare gefitinib with carboplatin/paclitaxel doublet chemotherapy given as first line treatment in terms of progression free survival (PFS). Secondary objectives included overall survival, objective tumour response rate, safety and tolerability, quality of life and symptom improvement. Exploratory objectives also involved investigation of baseline biomarker data to ascertain if there were any biomarkers that differentiate for a relative treatment effect when comparing the randomised treatment arms. Patients included were those with advanced NSCLC with adenocarcinoma histology who had never smoked or were ex-light smokers with a WHO performance status of 0-2 and had not received prior chemotherapy[1]. A total 1217 patients were randomised to the study. Gefitinib was administered in a dose of 250 mg orally, once daily, and carboplatin in a target dose using the area under the concentration versus time curve (AUC) of 5 or 6 (mg/mL.min) intravenous (IV) on day one every three weeks plus paclitaxel 200 mg/m^2 IV on day one every three weeks.

Additional data was also provided in this review essentially in summary form, relating to two independently run Phase III studies of gefitinib versus doublet chemotherapy in first line NSCLC patients (Study JP0056 and Study 0054). JP0056 compared gefitinib with carboplatin/paclitaxel in a prospective study of all EGFR mutation-positive patients including patients irrespective of histological smoking status, while study 0054 provided data from a comparison of gefitinib with gemcitabine/cisplatin in never-smokers with adenocarcinoma histology.

There were also two further Phase II clinical trials. INSTEP was conducted in 37 centres and involved a placebo-controlled randomised double blind parallel group Phase II trial

[1] WHO performance status. The World Health Organization (WHO) designed the scale which has categories from 0 to 4 as follows:
0 : fully active and more or less as you were before your illness
1 - cannot carry out heavy physical work, but can do anything else
2 - up and about more than half the day; you can look after yourself, but are not well enough to work
3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
4 - in bed or a chair all the time and need a lot of looking after

comparing gefitinib plus best supportive care with placebo plus best supportive care with the primary objective being assessment of progression free survival. Secondary objectives included overall response rate, overall survival and pulmonary symptom improvement, quality of life and tolerability. A total of 220 patients were recruited of whom 201 were randomised to study treatment. Gefitinib was administered in a dose of 250 mg orally once daily with matching placebo tablets. Patients enrolled had advanced non small cell lung cancer, were chemotherapy naive but had a poor performance status WHO PS 2 or 3 and were considered unfit for chemotherapy treatment.

The second Phase II trial was INVITE conducted in 41 centres and which was a randomised open label parallel group Phase II study with the primary objective to compare gefitinib and vinorelbine in terms of progression free survival, with secondary objectives including overall survival, overall response rate, quality of life and adverse event profile. Patients enrolled had advanced non small-cell lung cancer, were aged at least 70 years and had not received prior chemotherapy, biological or immunological therapies. A total of 196 patients were randomised onto this trial. Gefitinib was administered in a dose of 250 mg orally once daily and vinorelbine 30 mg/m^2 administered IV on days one and eight every three weeks.

Full reports of the three AstraZeneca studies were provided in this submission. Summaries only were provided for the two independent Phase III trials mentioned above (that is, study JP0056 and study 0054). Full data was provided for the two Phase II trials. All data were adequate for appropriate evaluation.

The proposed change to the second line indication also involved an evaluation of the INTEREST trial which was evaluated in a previous submission when an indication similar to the current proposed modified indication was rejected in June 2009.

Pharmacology

No new pharmacodynamic or pharmacokinetic data is presented in this submission.

Efficacy

Pivotal study

The pivotal trial IPASS was developed on the basis that earlier studies had demonstrated evidence of efficacy for gefitinib in patients with advanced NSCLC, including at least a Phase III study of gefitinib versus placebo (ISEL) which demonstrated evidence of higher response rates in EGFR mutation-positive patients for gefitinib[2]. The evidence also had suggested that response rate data were more favourable for females, never-smokers and Asian patients and in patients with adenocarcinoma as opposed to other tumour histologies. The selection of patients on basis of these factors were key aspects for the IPASS study design.

IPASS was a Phase III randomised open label first line therapy for gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced NSCLC. This was a multi-centre trial conducted in 87 centres throughout Asia.[3]

[2] Exploratory analysis of EGFR biomarkers was statistically inconclusive however response rates in ISEL were higher among IRESSA treated patients with EGFR mutation-positive tumours
[3] Mok, TS, Wu Y-L, Throngprasert S et al. Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med* 2009;361:947-57.

The primary objective of the trial was to compare gefitinib with carboplatin/paclitaxel doublet chemotherapy given as first line treatment in terms of evaluation of progression free survival (PFS) in selected non small cell lung cancer patients.

A series of secondary objectives were also involved, including comparing the randomised treatment arms in terms of overall survival, objective tumour response rate according to RECIST criteria, safety and tolerability profile of gefitinib at a 250 mg daily dose related to that of carboplatin/paclitaxel, quality of life as measured by total score and trial outcomes index (TOI) of the functional assessment of cancer therapy – lung cancer (FACT-L) questionnaire and symptom improvement as measured by the Lung Cancer Sub-scale (LCS) of the FACT-L questionnaire. [4], [5]

Exploratory objectives also included to investigate baseline biomarker data concerning patients to ascertain if there were any biomarkers that differentiate for a relative treatment effect when comparing the randomised treatment arms.

Thus the study population for IPASS was clinically selected and included patients from Asian countries with adenocarcinoma of the lung who either never smoked or were previously light smokers and patients who had stage IIIB or IV malignancy and had not received previous chemotherapy except for non-platinum based adjuvant chemotherapy. The doublet chemotherapy chosen for this trial was carboplatin/paclitaxel as this is a widely used regimen in Asia.

The dose of gefitinib chosen for this study was 250 mg/day as this has previously been identified as the optimum biological effective dose of gefitinib for patients with advanced NSCLC.

The carboplatin/paclitaxel regimen involved administration of carboplatin in AUC of 5 or 6 in conjunction with paclitaxel 200 mg/m^2 every 3 weeks.

Gefitinib was continued until patients had documented evidence of progressive disease or other criteria for discontinuation were met. Paclitaxel and carboplatin were continued for a total of six cycles. Chemotherapy was to be discontinued if there was objective progressive disease or other criteria for discontinuation were met.

Primary variable for assessment was PFS with secondary variables including objective tumour response rate as per RECIST, quality of life (FACT-L and TOI) and symptom improvement (LCS of FACT-L) as measured by the percentage of patients with improvement in FACT-L, FACT-L total, TOI and LCS scores and time to worsening in FACT-L total and TOI and LCS scores in survival without CTC grade III or IV toxicity.[6] An exploratory objective included investigation of baseline biomarker data in considering patients to ascertain if there are any biomarkers to differentiate for a relative treatment effect when comparing the randomised treatment arms.

All patients were required to have measurable disease and WHO performance status of 0–2.

The primary outcome variable (PFS) was to be analysed in the intention-to-treat (ITT) population in a proportional hazard's model and adjusted to WHO performance status (0,

[4] RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

[5] FACT-L: The Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument is a 44-item self-report which measures multidimensional quality of life. The total score results from adding the physical well being (PWB) subscore, the functional well being (FWB) subscore, the social well being (SWB) subscore, the emotional well being (EWB) subscore and additional concerns.

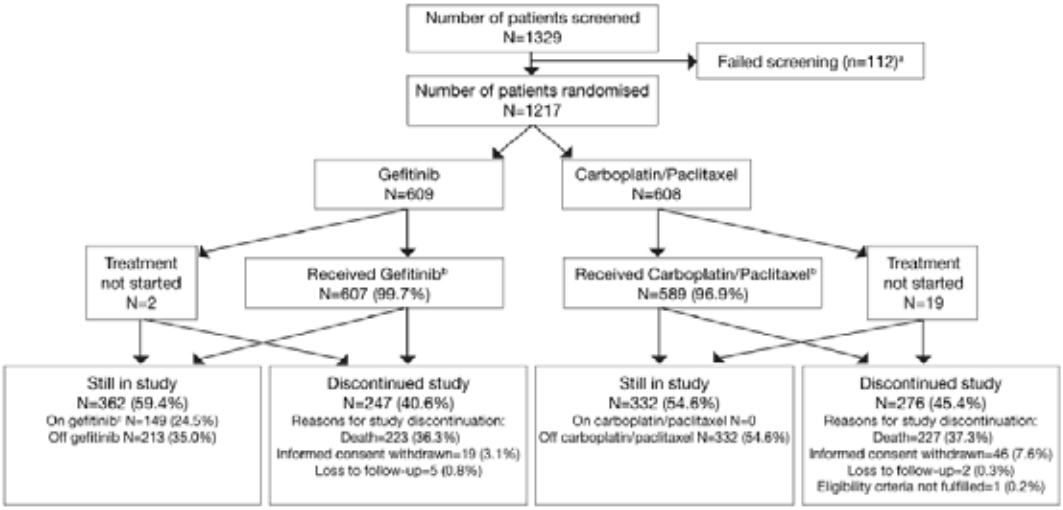
[6] LCS: Lung Cancer Subscore; Trial Outcome Index (TOI): combining scores on PWB, FWB and LCS

1 versus 2), smoking history (never versus light) and gender. The Hazard Ratio (HR) was estimated together with two-sided 95% confidence intervals (CI) and p-value. The Null Hypothesis of PFS inferiority would be rejected, hence non-inferiority concluded, if the upper 95% CI limit of HR lay below 1.2. In addition if the upper 95% CI limit of the HR lay below 1 then superior PFS of gefitinib over carboplatin/paclitaxel would be declared. A follow-up analysis of overall survival will be conducted at a later date when 944 deaths have occurred. Accordingly only an earlier analysis of overall survival is provided in this submission, this is considered to be somewhat premature.

A total of 1217 patients were randomised to treatment, 609 to gefitinib treatment and 608 to the doublet. The majority of patients were female (79%) with a median age being 57 years and the majority 93.7% of patients had never smoked. Almost all (99%) patients were Oriental of whom 51% were Chinese and 19% Japanese. A total of 64% of patients had WHO Performance Status (PS) 1 and 10% PS 2. The remainder had WHO PS 0 (26%). At diagnosis, 27% of patients had stage IIIB disease and 69% stage IV disease. The two treatment arms were well balanced at baseline with respect to demographic characteristics and tumour burden.

The disposition of patients is shown in Figure 1.

Figure 1: Disposition of patients in the IPASS Study



a Main reasons were: serum creatinine greater than 1.5 x upper limit of reference range or creatinine clearance less than or equal to 60 mL/min; newly diagnosed central nervous system metastases that had not yet been definitively treated with surgery and/or radiation; absolute neutrophil count less than 2.0 x 109/L, platelets less than 100 x 10^9/L or haemoglobin less than 10 g/dL.

b The safety analysis, conducted according to treatment received, was performed on this population.

c 63 (10.3%) patients that were treated with gefitinib and had disease progression received gefitinib after progression as the investigator considered it was providing benefit and 1 (0.2%) patient that was treated with carboplatin / paclitaxel and had disease progression continued received carboplatin / paclitaxel after progression as the investigator considered it was providing benefit.

AE: adverse event; DCO: Data cut-off date (14 April 2008); N: Number of patients

As might be expected the majority of patients on the doublet had completed chemotherapy by the time of study assessment. Adverse events accounted for treatment discontinuation in 6.9% of patients on gefitinib and 14.1% of patients on the doublet chemotherapy.

Of the 1217 patients randomised in the study, 683 patients provided samples for biomarker evaluation. The total number of patients with evaluable data was 437 (36%) for EGFR mutation analysis, 406 (33%) for EGFR and fluorescent in situ hybridisation (FISH) status analysis and 365 (30%) for EGFR protein expression analysis. A total of 329

patients had samples evaluable for all three biomarkers including 31 patients with samples that were negative for three biomarkers and 298 patients with samples that were positive for one or more biomarkers. Key demographic and baseline characteristics for patients with evaluable tissue samples are generally comparable to the demographics for the ITT population.

The median duration of follow up for the whole study population at the time of data analysis (14 April 2008) revealed that for the analysis of PFS the median duration was 5.6 months in both treatment arms. The analysis of PFS was due to be performed when 944 progressions had accrued in the ITT population, however the analysis conducted was based upon a total 950 progressions (78% to maturity).

The study exceeded its primary objective of non-inferiority and demonstrated superiority of gefitinib relative to carboplatin/paclitaxel in terms of progression free survival with an HR 0.74 ($p<0.0001$) as illustrated in Table 1. The risk of progression over a given period was reduced by 26% on gefitinib compared with the doublet, which translates to a 35% prolongation in PFS.

As indicated in Figure 2, the HR was not constant over time with a probability of being progression free in favour of the doublet chemotherapy in the first six months and in favour of gefitinib in the following 16 months. As will be demonstrated below, this appears to relate to mutation status.

Median PFS is 5.7 months and 5.8 months respectively for patients in the gefitinib and chemotherapy arms as indicated in Table 2.

Table 1: PFS in IPASS

Analysis	N	Number (%) Progressed		Hazard ratio[a]	95% CI	p-value
Primary ITT analysis[b]						
Gefitinib	609	453	(74.4)	0.741	0.651, 0.845	<0.0001
Carboplatin/ paclitaxel	608	497	(81.7)			
Supportive PP analysis[b]						
Gefitinib	597	446	(74.7)	0.743	0.652, 0.848	<0.0001
Carboplatin/ paclitaxel	580	489	(84.3)			
Supportive ITT analysis: Unadjusted for covariates						
Gefitinib	609	453	(74.4)	0.735	0.645, 0.838	<0.0001
Carboplatin/ paclitaxel	608	497	(81.7)			
Supportive ITT analysis: Censoring events occurring >12 weeks after previous adequate RECIST assessment[c]						
Gefitinib	609	444	(72.9)	0.745	0.653, 0.850	<0.0001
Carboplatin/ paclitaxel	608	484	(79.6)			
Supportive ITT analysis: Censored before the start of additional anti-cancer therapy[d]						
Gefitinib	609	442	(72.6)	0.737	0.645, 0.843	<0.0001
Carboplatin/ paclitaxel	608	467	(76.8)			

Data from Table 17 IPASS CSR

[a] Hazard ratios derived from Cox proportional hazards model with covariates for randomised treatment, sex, WHO performance status and smoking history: a HR <1 implies a lower risk of progression over a given period with gefitinib compared with carboplatin / paclitaxel. The non-inferiority margin was HR 1.2.

[b] The primary ITT and the PP analyses includes all progression events, or deaths in the absence of progression, regardless of when they occurred.

[c] The secondary ITT analysis does not include progression events, or deaths in the absence of progression which occur more than 12 weeks after the last evaluable RECIST assessment.

[d] The secondary ITT analysis does not include progression events, or deaths in the absence of progression that occurred after the start of additional anti-cancer therapy. Patients who are progression free are also censored before the start of additional anti-cancer therapy.

CI: Confidence interval; ITT: Intention-to-treat; PFS: progression free survival; PP: Per-protocol; RECIST: Response Evaluation Criteria in Solid Tumours

Figure 2: Kaplan-Meier curves for the primary analysis of PFS

Figure 3 **Kaplan-Meier curves for the primary analysis of PFS (IPASS, ITT Population)**

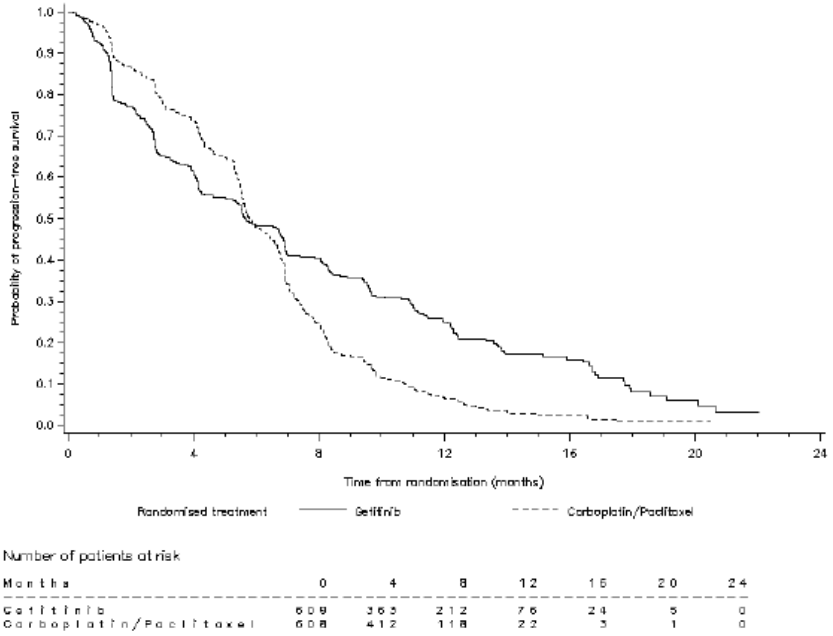


Table 2: Summary of PFS

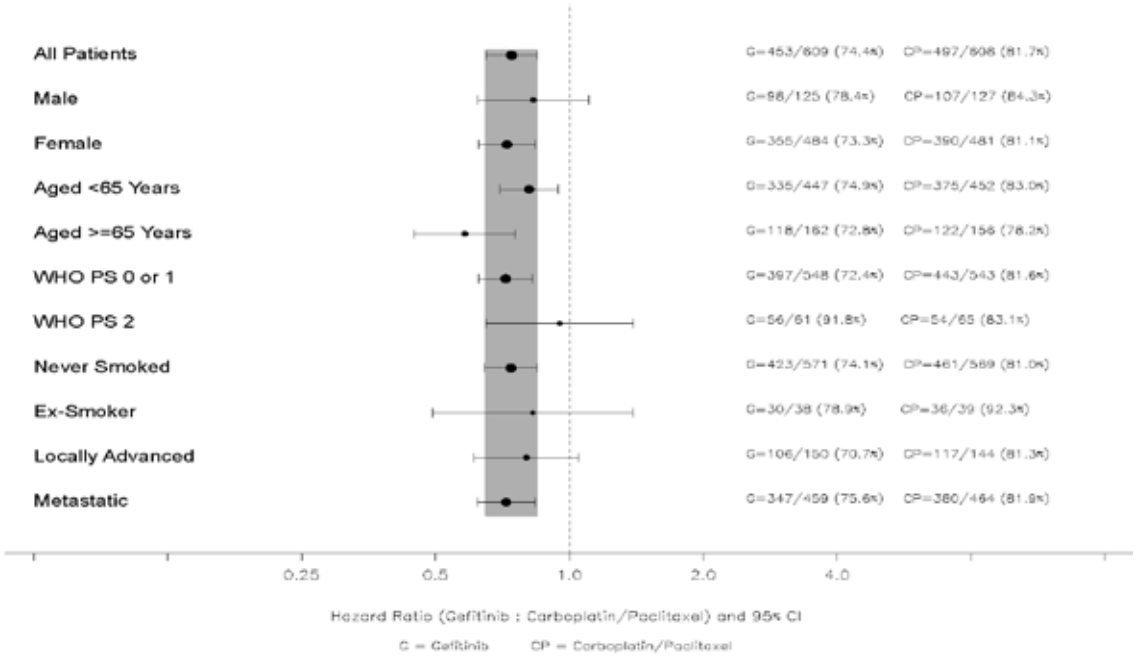
Progression-free survival	Gefitinib (N=609)	Carboplatin / Paclitaxel (N=608)
Number (%) progressed	453 (74.4)	497 (81.7)
Median PFS (months)[a]	5.7	5.8
4-month progression-free rate (%)[a]	60.6	73.7
6-month progression-free rate (%)[a]	48.3	47.6
12-month progression-free rate (%)[a]	24.9	6.7

Data from IPASS CSR Table 18
[a] Calculated using the Kaplan-Meier Technique.
ITT: Intention-to-treat; N: Number of patients; PFS: progression free survival

Several sub-group analyses had been planned and these included pre-specified factors of gender, age, WHO performance status, smoking status and disease status. In all sub-groups tested, PFS was statistically or numerically longer in gefitinib compared with the doublet chemotherapy as indicated in Figure 3.

Review of secondary efficacy variables revealed that in relation to overall survival (OS), a total of 450 patient deaths had occurred by the time of study evaluation or a 37% maturity. Follow up of these patients is still ongoing and the final analysis is planned when 944 deaths have occurred. The median duration of follow up for OS at present was 11.6 months. OS was similar in both treatment groups as of this evaluation with a median survival of 18.6 months in the gefitinib arm and 17.3 months in the carboplatin/paclitaxel arm.

Figure 3: Analysis of PFS by Subgroup



HRs <1 indicates a difference in favour of gefitinib while HRs >1 favour carboplatin / paclitaxel.
The size of the point estimate reflects the number of events in the subgroup with a larger circle indicating more events; the grey band represents the confidence interval (CI) for the overall (all patients) HR.
ITT: Intention to treat; PS: performance status; WHO: World Health Organisation

In relation to assessment of objective tumour response rate, the response rate was significantly higher in the gefitinib arm being 43% compared to the doublet arm of 32% with a p-value of 0.0001.

Sub-group analyses performed in relation to other factors namely, gender, age, WHO performance status, smoking status and disease status illustrated that the overall response rate was numerically or statistically greater for gefitinib than carboplatin/paclitaxel treatment for all these sub-groups and was consistent with the PFS results.

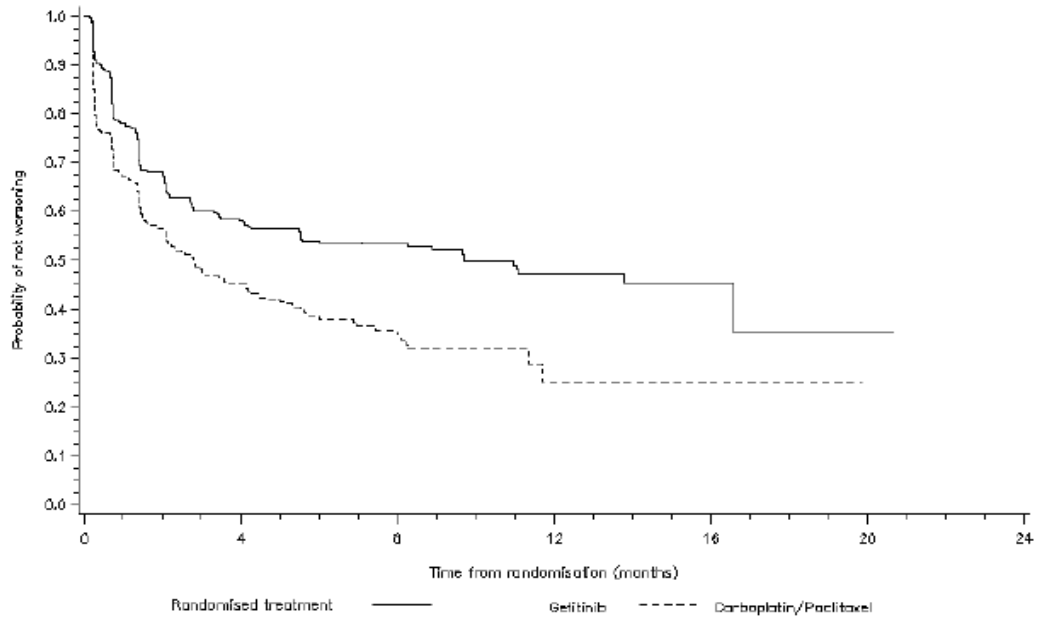
In relation to assessment of quality of life criteria in the overall population compliance for completion of the FACT-L questionnaire was generally high. In the overall population significantly more gefitinib-treated patients experienced clinically relevant improvements in quality of life as measured by both FACT-L and TOI compared with doublet chemotherapy. However similar percentages of patients on both treatment arms experienced an improvement in disease related symptoms as measured by LCS.

In the overall population, times to worsening quality of life and disease related symptoms were substantially longer in the gefitinib arm compared with the doublet chemotherapy arm with a median of 7.1 – 9.7 months for gefitinib and 2.5 – 3.1 months with doublet chemotherapy. The Kaplan-Meier curve for time to worsening in TOI score is shown in Figure 4.

Analysis of PFS biomarker status showed that the treatment effect was significantly different between patients with EGFR mutation-positive and -negative tumours (treatment by mutation status interaction test p<0.0001) and between patients with EGFR FISH-positive and -negative tumours (treatment by EGFR FISH interaction test p=0.0437). A Forest Plot displaying the analysis by biomarker status is shown in Figure 5.

Figure 4: Kaplan-Meier curves for time to worsening in TOI scores

Figure 6 Kaplan-Meier curves for time to worsening in TOI score (IPASS, EFQ Population)

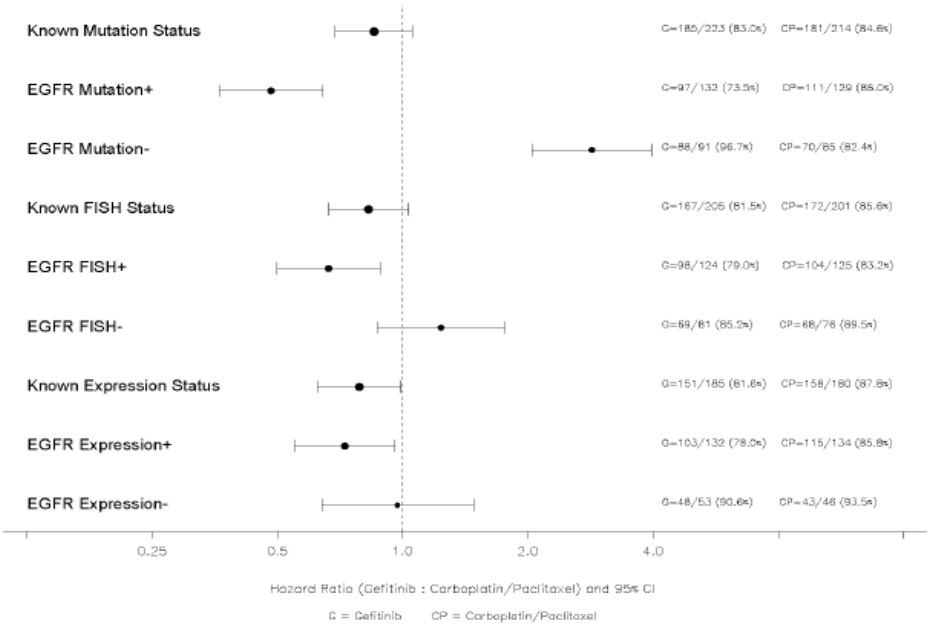


Number of patients at risk:

Months	0	4	8	12	16	20	24
Gefitinib	590	247	128	36	11	2	0
Carboplatin/Paclitaxel	561	176	37	7	1	0	0

Figure 5: Analysis of PFS by biomarker status

Figure 8 Analysis of PFS by biomarker status (IPASS, ITT Population)



HRs <1 indicates a difference in favour of gefitinib while HRs >1 favour carboplatin / paclitaxel.
The size of the point estimate reflects the number of events in the subgroup with a larger circle indicating more events.
EGFR: epidermal growth factor receptor; FISH: fluorescence in situ hybridisation.

A very strong relationship between the EGFR mutation status and PFS outcome was evident as indicated in Table 3. PFS was significantly longer with gefitinib than

carboplatin/paclitaxel treatments in patients who were EGFR mutation-positive with a median of 9.5 months versus 6.3 months. In contrast PFS was significantly shorter for gefitinib than carboplatin/paclitaxel treatment in patients who are EGFR mutation-negative (1.5 months versus 5.5 months, p<0.0001). The results in the mutation-unknown group were similar to that for the ITT population as might be expected, with an HR of 0.68 and p< 0.0001.

An evaluation of OS by mutation status was also performed recognising there would only be a small number of events in this analysis. The figures were not significantly different for either the mutation-positive or mutation-negative groups as might be expected.

Review of improvement rates in relation to quality of life for the mutation sub-populations revealed that they were significantly in favour of gefitinib compared with the doublet chemotherapy in patients with EGFR mutation-positive status. In contrast improvement rates for quality of life and in lung cancer symptoms were in favour of carboplatin/paclitaxel compared with gefitinib in patients with EGFR mutation-negative status.

Time to worsening and quality of life and disease related symptoms were substantially longer in the gefitinib arm compared with the doublet chemotherapy arm in patients with EGFR mutation-positive status, ranging in a median of 11.3 – 16.6 months for gefitinib and 2.9 – 3.0 months with doublet chemotherapy. Again in contrast, times to worsening in quality of life and disease-related symptoms were similar or shorter in the gefitinib arm compared with the doublet chemotherapy arm with EGFR mutation-negative status with a median of 1.4 months for gefitinib and 1.4 – 4.2 months with chemotherapy.

Table 3: Analysis of clinical outcomes according to EGFR mutation status

EGFR mutation	Gefitinib		Carboplatin / paclitaxel		Hazard ratio/ Odds ratio[a]	2-sided 95% CI	p-value
	N	Number (%) events	N	Number (%) events			
Progression-free survival							
Known	223	185 (83.0)	214	181 (84.6)	0.853	0.690 to 1.055	0.1426
M+	132	97 (73.5)	129	111 (86.0)	0.482	0.362 to 0.642	<0.0001
M-	91	88 (96.7)	85	70 (82.4)	2.853	2.048 to 3.975	<0.0001
Unknown	386	268 (69.4)	394	316 (80.2)	0.684	0.579 to 0.808	<0.0001
Objective response rate[b]							
Known	223	95 (42.6)	214	81 (37.9)	1.212	0.825 to 1.780	0.3268
M+	132	94 (71.2)	129	61 (47.3)	2.751	1.646 to 4.596	0.0001
M-	91	1 (1.1)	85	20 (23.5)	0.036	0.005 to 0.273	0.0013
Unknown	386	167 (43.3)	394	115 (29.2)	1.877	1.390 to 2.534	<0.0001

Data from IPASS CSR Table 30

[a] HRs derived from Cox proportional hazards model with covariates for randomised treatment, sex, WHO performance status and smoking history: a HR <1 implies a lower risk of progression/death over a given period with gefitinib compared with carboplatin / paclitaxel. Odds ratio derived from logistic regression model with covariates; odds ratios >1 indicate a greater chance of response with gefitinib than carboplatin / paclitaxel.

[b] Objective tumour response defined as CR+PR.

CI: Confidence interval; EGFR: epidermal growth factor receptor; M+: EGFR mutation positive; M-: EGFR mutation negative; N: Number of evaluable patients.

The relationship between EGFR, FISH status and PFS outcome was evident. PFS was significantly longer with gefitinib than doublet chemotherapy in patients who had FISH-positive tumours with an HR of 0.66 (p=0.005). In contrast PFS was numerically shorter with gefitinib than chemotherapy in patients who had FISH-negative tumours with an HR

of 1.24 (p=0.2368). Results in the FISH status unknown group showed an HR of 0.70 (p<0.0001) and was similar to those of the overall population as expected. Overall response rates by EGFR FISH status were consistent with PFS results by EGFR FISH status.

A post-hoc analysis was performed to investigate whether the PFS effect in the patients with EGFR FISH-positive tumours were due to the overlap of EGFR FISH status with EGFR mutation status. Of the 245 patients with EGFR FISH-positive tumours with EGFR mutation status also known, 190 patients (78%) also had a positive EGFR mutation status.

PFS was longer with gefitinib than chemotherapy in patients who had FISH-positive and mutation-positive tumours (HR: 0.48). In contrast PFS was shorter with gefitinib than chemotherapy in patients who had FISH-positive tumours with no EGFR mutation detected (HR: 3.85). This suggests that the PFS benefit seen in the sub-group of patients with FISH-positive tumours was driven by the overlap with positive mutation status.

There was no relationship evident between EGFR protein expression status and PFS outcome with a treatment by EGFR protein expression status interaction test of p=0.2135. PFS was significantly longer for gefitinib than chemotherapy in patients who were EGFR protein expression-positive. There was no significant difference in PFS between treatments in patients who were EGFR protein expression-negative. Results for the EGFR protein expression unknown group was similar to that for the ITT population as expected. Overall response rate results by EGFR protein expression status was consistent with the PFS results by EGFR protein expression status and numerically favoured gefitinib in both EGFR protein expression-positive and -negative sub-groups.

Evaluator's comment

The IPASS study is a large one and results for the primary efficacy variable, namely PFS clearly indicates superiority for gefitinib versus standard doublet chemotherapy in patients with adenocarcinoma, ex-light or never-smokers and stage IIIB/IV lung cancer. The benefits in overall PFS are also seen in the various sub-groups. Also of added interest is the fact that quality of life criteria tended to benefit patients receiving gefitinib versus chemotherapy. Importantly the biomarker data indicates that the particular reason for this benefit of gefitinib relates to the EGFR mutation-positive sub-set of patients. This is biologically rational and indicates that the EGFR tyrosine kinase inhibitor has clinical benefit. The evaluator considered the data sufficiently robust to support the fact that gefitinib is an appropriate first line treatment for EGFR mutation-positive patients with stage IIIB/IV lung cancer who have not received prior chemotherapy.

Supporting studies

Limited data from two independently run Phase III trials were presented in this submission which involves the administration of gefitinib versus doublet chemotherapy in first line NSCLC. These are study JP0056 and study 0054.

Study JP0056

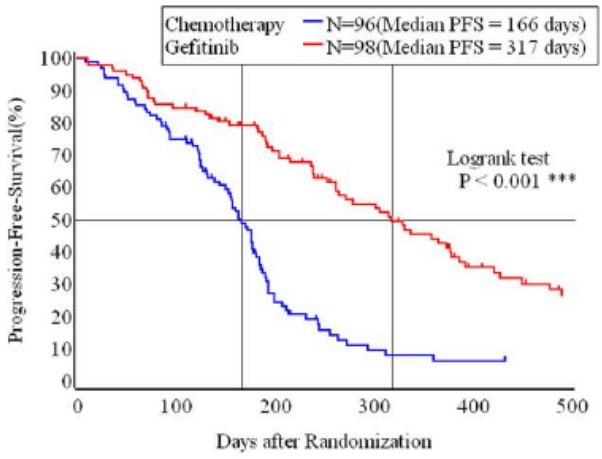
Study JP0056 was a randomised Phase III collaborative group study comparing efficacy and safety of gefitinib with carboplatin/paclitaxel doublet chemotherapy in EGFR mutation-positive patients with stage IIIB/IV NSCLC unselected by histological or smoking status. The study was conducted in Japan. The primary endpoint was PFS with secondary endpoints OS, response rate, quality of life and toxicity. Patients were assigned to receive either gefitinib 250 mg daily orally or IV administration of carboplatin AUC 6 and paclitaxel 200 mg/m^2 respectively in a 21 day cycle. After initial disease progression further treatment was at the discretion of the treating physician. Data cut-off was December 2008.

Study JP0056 was designed to include 320 EGFR mutation-positive chemotherapy naïve stage IIIB/IV NSCLC patients with ECOG Performance Status 0-1.[7] The data cut-off for the interim analysis of PFS in study JP0056 included a total of 200 patients: 99 were assigned to receive gefitinib and 101 to receive chemotherapy. Patient characteristics were generally well balanced between treatment arms in terms of gender, age, performance status and types of EGFR mutations. There were slightly more non-smokers in the gefitinib arm, (65% versus 58%) and slightly more patients with adenocarcinoma (90% versus 96%) and stage IIIB patients (18% versus 11%) in the carboplatin/paclitaxel arms.

Review of efficacy data for study JP0056 revealed the limited data available from the planned interim efficacy analysis with 98 patients treated with gefitinib and 96 with chemotherapy who were included in the analysis of the primary efficacy PFS endpoint. The PFS was shown to be significantly longer for gefitinib-treated patients compared with the chemotherapy patients with an HR of 0.357 ($p<0.001$ by log rank test). The median PFS was 10.4 months versus 5.5 months favouring gefitinib and this is illustrated in Figure 6. A significantly higher overall response rate was obtained in the gefitinib arm compared with the chemotherapy arm being 74.5% versus 29% with $p<0.001$ by Fishers Exact Test.

Figure 6: Kaplan-Meier curves for PFS: overall population

Figure 26 Kaplan-Meier curve for PFS: overall population (Study JP0056, ITT population)



Study 0054

Study 0054 was a randomised Phase III study conducted to compare the efficacy and safety of gefitinib as a first line treatment with gemcitabine plus cisplatin as standard chemotherapy in never-smokers with lung adenocarcinoma. The study was conducted in Korea. The primary endpoint was OS with secondary endpoints PFS, response rate and toxicity. In this study 309 never smokers with chemotherapy naive stage IIIB/IV lung

[7] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

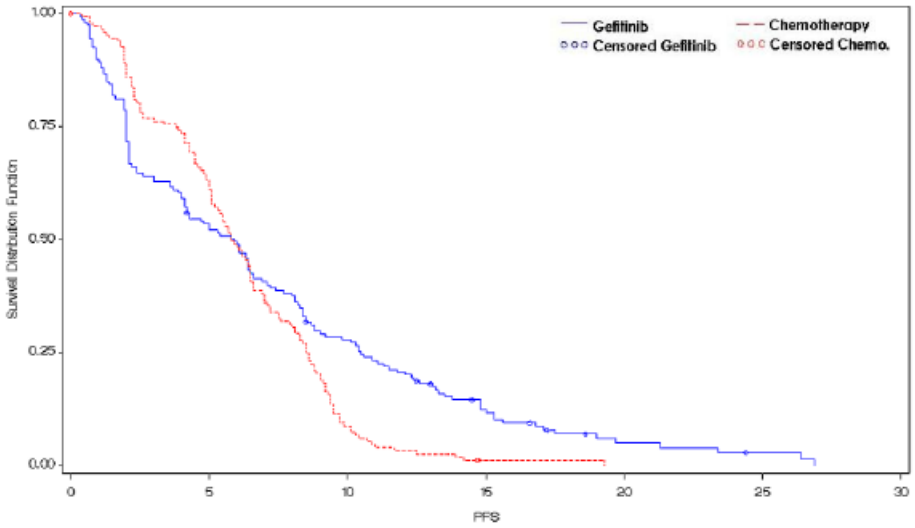
adenocarcinoma, ECOG performance status 0-2 and adequate organ function, were assigned to receive either gefitinib 250 mg/day orally (N=159) or chemotherapy with gemcitabine 1250 mg/m^2 on Day 1 and 8 with cisplatin 80 mg/m^2 on Day 1 every three weeks for up to nine courses (N=150). After initial disease progression further treatment was at the discretion of the treating physician.

Of the 309 patients, 159 were assigned to receive gefitinib and 150 assigned to receive chemotherapy. No information was available on the median exposure to treatment. Information on the imbalance of treatment groups and of concomitant medications administered for the 159 patients assigned to receive gefitinib and the 150 patients assigned to receive chemotherapy was not available.

Review of data available demonstrated that gefitinib-treated patients had better PFS [HR 0.813, 95% CI 0.641 to 1.031, 1-sided p=0.044 by log-rank test] and the Kaplan-Meier curves for PFS on both treatments crossed over around the median time, being 6.1 months versus 6.6 months for gefitinib versus chemotherapy and this is illustrated in Figure 7. This was similar to that observed with the IPASS study. The study concluded that the crossing over of the PFS curve reflected the differences in PFS by EGFR mutation status.

Figure 7: Kaplan-Meier curves for PFS: overall population

Figure 27 Kaplan-Meier curves for PFS: overall population (Study 0054, ITT population)



In patients with EGFR mutation-positive status (N=42), the PFS was numerically longer for gefitinib-treated patients with an HR of 0.613 (95% CI 0.308 to 1.221, p=0.084); median 8.4 months vs 6.7 months. In patients with EGFR mutation-negative status (N=54) the PFS was shorter for gefitinib-treated patients compared to the chemotherapy with an HR of 1.517 (95% CI 0.880 to 2.615, p=0.071); median 2.1 months vs 6.4 months.

OS data was similar between the two treatment arms. The median and one year survival rates were 21.3 months and 74.2% for the gefitinib arm and 23.3 months and 76.2% for the chemotherapy arm respectively. This was considered to be mainly due to the fact that 80.7% of the chemotherapy arm patients received gefitinib during their subsequent course. Follow up for overall survival is ongoing.

Evaluator's comment

These data do provide some support for the pivotal IPASS study. Again there is clear evidence of benefit for gefitinib in chemotherapy naïve patients who are EGFR mutation-positive with additional numbers in two independent trials tending to reinforce the positive potential for gefitinib in this group of patients.

Other supporting studies

Two other Phase II studies were presented in this submission (that is, study INSTEP and study INVITE). Both were designed to provide a preliminary evaluation of the efficacy and safety of gefitinib 250 mg monotherapy in first line NSCLC treatment setting versus placebo and versus vinorelbine, respectively. The studies focus on different elements of the broad spectrum of first line patients observed in clinical practice. Both studies were international multi-centre randomised parallel group Phase II studies utilising standard efficacy and safety endpoints with patients allocated to treatment on a one to one basis. INSTEP was double blind and placebo-controlled and was designed to provide a preliminary evaluation, however the addition of gefitinib 250 mg once daily to best supportive care confirmed an improvement in PFS in chemotherapy naïve patients with advanced stage IIIB or IV NSCLC or a poor performance status (WHO PS 2 or 3) and were considered unfit for chemotherapy treatment.[8] In contrast INVITE was an open label study designed to compare PFS as primary variable for gefitinib compared with vinorelbine in chemotherapy naïve elderly patients with locally advanced stage IIIB or metastatic stage IV NSCLC.[9] Both studies provided evidence of some preliminary indication of efficacy for gefitinib in a chemotherapy naïve patient population, but there was insufficient data available from these studies to evaluate outcome by EGFR mutation status.

The study entry criteria for INSTEP defined a target patient population of patients aged 18 years or older with histologically or cytologically confirmed advanced stage IIIB or IV NSCLC who were chemotherapy naïve and were considered unfit for chemotherapy treatment. Patients were required to have measurable disease according to RECIST criteria and poor performance status WHO PS = 2 or 3.

The study entry criteria for INVITE included a target population of patients aged at least 70 years with histologically confirmed locally advanced stage IIIB or metastatic stage IV NSCLC who had not received prior chemotherapy, biological or immunological therapy. Patients were required to have measurable disease according to RECIST criteria and WHO PS of 2 or less and were prepared to provide a histological biopsy sample from the original tumour or metastatic site for biomarker analysis. In both INSTEP and INVITE a number of other eligibility criteria ensured safety of patients who entered this study.

A total of 201 patients were randomised to treatment in the INSTEP study including 100 patients receiving gefitinib 250 mg and 101 patients to receive placebo. These patients were recruited from 37 centres in five countries. Approximately 39% of patients were female, 9.5% were never-smokers, 37% had adenocarcinoma histology and 3.5% were of Oriental racial origin. The median age of patients was 74 (range 42-90) years. The two treatment groups were well balanced at baseline with respect to all important factors. The number of major protocol deviations was similar between the two treatment arms being 12% in the gefitinib arm and 10.9% in the placebo arm.

[8] Goss G, Ferry D, Wierzbicki R et al. Randomised Phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. *J Clin Oncol* 2009; 27: 2253-2260.

[9] Crino L, Cappuzzo F, Zatloukal P et al. Gefitinib versus vinorelbine in chemotherapy- naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomised Pahse II study. *J Clin Oncol* 2008; 26: 4253-4260.

The patients who participated in INVITE included a total of 196 patients from 41 centres in 10 countries of whom 97 were randomised to gefitinib and 99 patients to vinorelbine. Tumours tended to be either squamous cell carcinoma (46.4%) or adenocarcinoma (40.3%) and more patients had metastatic (77%) than locally advanced (23%) disease. Approximately 16% of the patients were Oriental. The median age was 74 (range 70-89) years. Demographic and patient characteristics were generally reasonably balanced. The number of major protocol deviations was low being 7.7% overall and well balanced between the treatment groups.

Review of results from the INSTEP study revealed that gefitinib showed some improvement compared to placebo in terms of PFS, objective response rate and OS although this did not reach statistical significance. The HR for the comparison of PFS between gefitinib and placebo was 0.821 (p=0.2165). The odds ratio for the comparison of objective response rate between gefitinib and placebo was 6.566; objective tumour responses were achieved for six patients and one patient in the gefitinib and placebo groups respectively. The HR for the comparison of OS between gefitinib and placebo was 0.840 (p=0.2722).

Review of biomarker data relating to assessment of EGFR FISH analyses revealed that the EGFR FISH positivity, that is, a high EGFR gene copy number appeared predictive for a gefitinib effect over placebo. Of the patients with known EGFR FISH status the sub-group of 32 (38.1%) EGFR FISH-positive patients had superior PFS (HR 0.288) and numerically improved OS (HR 0.437) when treated with gefitinib as opposed to placebo. Of the patients with known EGFR FISH status there was no strong evidence of a difference in efficacy between gefitinib and placebo for the sub-group of 52 patients with a low EGFR gene copy number (EGFR FISH-negative). The HR for the comparison of PFS between gefitinib and placebo was 0.74; HR for overall survival was 1.022.

Further analyses of these data suggest that the sub-group EGFR FISH-positive patients appear to achieve better clinical outcomes than the sub-group EGFR FISH-negative patients when treated with gefitinib, although this is a non-randomised comparison. The HR for the comparison of PFS between EGFR FISH-positive patients and the EGFR FISH-negative patients was 0.262 and the HR for the comparison of OS between EGFR FISH-positive patients and EGFR FISH-negative patients is 0.468.

Review of quality of life data for the INSTEP study revealed symptom improvement rates were similar for both gefitinib and placebo treated patients with gefitinib 28.3% improved and placebo 28.3% improved. Comparison of lung cancer symptoms between gefitinib was 32.9% improved and placebo 30.8% improved respectively. Overall patients reported functionality of quality of life improvement rates were similar in gefitinib and the placebo treated groups, with TOI for gefitinib 15.8% improved and placebo 13.8% improved while the comparison of FACT-L total score between gefitinib with 21.1% improved and placebo 20% improved.

Review of efficacy results from the INVITE study revealed that gefitinib was broadly similar to the vinorelbine in terms of clinical efficacy in the ITT population. The HR ratio for the comparison of PFS between gefitinib and vinorelbine was 1.185 (p-value = 0.3095) with 80.4% progressed for gefitinib compared to 78.8% progressed for vinorelbine. This represented a slight numerical advantage for vinorelbine but there was no significantly statistically difference between the groups. The objective response rates were achieved in three patients within the gefitinib group and five patients in the vinorelbine groups. HR for the comparison of OS survival treated with gefitinib and vinorelbine was 0.984.

Patients who were FISH-positive and who were treated with gefitinib had a non-significant trend toward poorer PFS and OS outcomes than patients who were FISH-negative and who were treated with gefitinib. Conversely, patients who were FISH-positive and who were treated with vinorelbine had a non-significant trend toward

improved PFS and OS outcomes than patients who were FISH-negative and who were treated with vinorelbine

Furthermore gefitinib-treated FISH-positive patients appeared to have worse PFS and OS than any other sub-group, including gefitinib-treated FISH-negative patients. There were too few patients available for analyses in other biomarkers.

Review of quality of life data revealed that consistent with efficacy results, symptom improvement rates were similar with gefitinib and vinorelbine, gefitinib being 36.6% improved and vinorelbine 31% improved and lung cancer symptoms were gefitinib 42.9% improved and vinorelbine 39.1% improved. Consistent with the more favourable tolerability profile of gefitinib compared with vinorelbine, overall quality of life improvement rates were higher with gefitinib than vinorelbine with gefitinib 22.9% improved and vinorelbine 6.3% improved. For the comparison of FACT-L total score, gefitinib was 24.3% improved with vinorelbine being 10.9% improved.

Evaluator's comment

These two Phase II studies add relatively little to the consideration of the proposed new indication. There were inadequate numbers of patients in either study in relation to EGFR mutation status for analyses. There does appear to be some small advantages for gefitinib over placebo in poor performance status patients but the numbers are relatively small and the data insignificant. In relation to older patients it would appear to be at least equivalent low levels of efficacy for gefitinib and vinorelbine. The data in fact really indicate minimal benefit in terms of response and influence on PFS with these two single agents in this patient population. However this is a small patient population and not specifically directed at EGFR mutation status thereby rendering the data of relatively little use.

Previous evaluation

Although not evaluated in this submission, the proposal to modify the second line indication relies on the INTEREST trial which was evaluated in the previous submission. For completeness, a summary of this trial is provided.

The main study in that previous submission was the Phase III, randomised, open-label, parallel-group INTEREST study in 1466 patients with locally advanced or metastatic recurrent NSCLC who had previously received platinum based-chemotherapy and were eligible for further chemotherapy with docetaxel; 1466 patients were randomised to oral gefitinib 250 mg once daily or intravenous docetaxel 75mg/m^2 every 3 weeks and the primary endpoint was OS.[10] Results from the INTEREST study were supported by 3 other randomised controlled studies with similar design to INTEREST, comparing gefitinib to docetaxel (V-15-32, SIGN and ISTANA). Based on the results of all seven studies in patients with pre-treated NSCLC (IDEAL I&II, ISEL, INTEREST, V-15-32, SIGN and ISTANA), the rationale to continue to limit the current indication to be more restrictive than 'treatment of NSCLC patients who have received prior chemotherapy' was considered to be no longer valid by the sponsor.

In the INTEREST trial, the non-inferiority criterion for OS was met (Table 3A). Other measures were supportive of similar efficacy with Iressa and docetaxel. Iressa or docetaxel were given until disease progression or unacceptable toxicity. The median age of patients was 60 (range 20-84) years. Patients had previously received platinum-based chemotherapy and were eligible for further chemotherapy. The median duration of treatment with Iressa was 2.4 (range 0-33) months and with docetaxel 2.8 (range 1-18)

[10] Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised Phase III trial. *Lancet* 2008; 372: 1809-18.

months. The trial was conducted in 24 countries in Europe, Asia and North, Central and South America.

An analysis of OS in the intent-to-treat population (n=733 in each treatment group) showed similar results as the primary analysis in the per-protocol population, confirming the robustness of the results.

OS was no better between either treatment arm in Asian patients versus non-Asians receiving Iressa versus docetaxel nor in never smokers versus smokers receiving Iressa versus docetaxel, unlike in the previous ISEL trial. The ISEL trial of Iressa 250 mg per day versus placebo failed to show a significant increase in survival with Iressa but did show significant benefit in the Asian and never-smoker sub-groups. The ISEL result led to the indication being restricted to patients who had never smoked. The ISEL study population was more refractory to chemotherapy than the INTEREST study population: 90% versus 58% of subjects had recurrent or progressive disease while receiving or within 90 days of their last chemotherapy dose, which may explain the non-significant overall result.

Whilst the quality-of-life results favour Iressa, there is a potential for bias since the trial was non-blinded. Compliance with the quality-of-life assessment was low with only 66% of subjects being evaluable. This was stated to be due to technical problems with the electronic diary used for collecting the data.

In the clinical evaluators opinion, three other trials of Iressa versus docetaxel in NSCLC, V-15-32, SIGN and ISTANA, did not provide useful efficacy data.

The clinical evaluator recommended approval for a more restricted indication:

Iressa is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), who had progressive or recurrent disease following previous chemotherapy and were eligible to receive further chemotherapy.

Table 3A: INTEREST – Efficacy Results

	Docetaxel iv 75 mg/m² q3w n=657	**Iressa po 250 mg daily n=659**	**Hazard or Odds Ratio[1] [95% CI]**
Progression-Free Survival median *mths – EFR*	2.7	2.2	1.05[2] [0.93, 1.18]
Overall Surviv median *mths - PPal*	8.0	7.6	1.020[2] [0.905, 1.150][3]
Overall Response Rate[4] *% - EFR*	7.6	9.1	1.23[5] [0.82, 1.84]
FACT Quality-of-Life Improved Incidence[6] *%*	n=476	n=490	
FACT-L	15	25	1.99[5] [1.42, 2.79]
TOI	10	17	1.82[5] [1.23, 2.70]
LCS	17	20	1.29[5] [0.93, 1.79]

PP: Per Protocol. EFR: Evaluable for Response = PP + unidimensional measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST). FACT: Functional Assessment of Lung Cancer. FACT-L: Lung Scale, TOI: Trial Outcome Index, LCS: Lung Cancer Subscale.

[1] Adjusted logistic regression estimate for Iressa/docetaxel.

[2] Hazard Ratio (> 1.0 favours docetaxel).

[3] Non-Inferiority Criterion: CI Upper limit < 1.154 – worked out using an effect retention approach discussed with US FDA; 96% CI in accordance with pre-planned Hochberg procedure for α since the co-primary analysis of the high EGFR gene copy number (EGFR FISH+) sub-group failed to reach statistical significance at the 5% level.

[4] RECIST criteria.

[5] Odds Ratio (> 1.0 favours Iressa).

[6] [3] 6-point increase in FACT-L and TOI and ≥ 2-point increase in LCS maintained for [3] 21 days.

Safety

Pivotal Study

The key study contributing safety data in the submission was the IPASS study, a small amount of safety data was also available from the two independent Phase III trials (JP0056, 0054) as well as data from the Phase II studies INSTEP and INVITE.

As indicated in the *Efficacy* section, gefitinib was administered to patients randomised to this arm in a dose of 250 mg/day orally until evidence of disease progression or other criteria warranting ceasing the agent. Safety and tolerability data were evaluated for these patients up to the data cut-off point on the 14 April 2008.

The nature, incidence and severity of adverse effects were assessed and categorised according to overall criteria of adverse events, serious adverse events and graded according to CTC criteria.[11] Also documented were incidences and reasons for study dose interruptions and withdrawals. Laboratory assessments including standard haematology and biochemistry were performed.

An overview of exposure in the IPASS study in terms of duration of treatment is presented in Table 4. Reflective of the different dosing regimens and tolerability profiles, overall exposure to first line study treatment was longer with gefitinib than the chemotherapy arm. The mean duration of treatment for gefitinib was 6.4 (range 0.1 – 22.8, median 5.6) months and 3.4 (range 0.7 – 5.9, median 4.1) months for carboplatin/paclitaxel. A higher percentage of gefitinib treated patients received treatment for longer than six months, that is, 47.6% compared with none in the chemotherapy group[12]. It is noteworthy that the mean dose intensity of chemotherapy was 92% for both carboplatin/paclitaxel indicative of generally reasonable tolerance to these agents.

Dose modifications due to toxicity were less common in patients treated with gefitinib (16.1%) compared with carboplatin/paclitaxel (35.2%/37.5%).

[11] **Common Terminology Criteria** (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

[12] Chemotherapy group only allowed maximum 6 cycles according to protocol

Table 4: Overall duration of exposure to gefitinib or carboplatin/paclitaxel

Table 3 Overall duration of exposure to gefitinib or carboplatin/paclitaxel (including dose interruptions) (IPASS, EFS population)

Exposure[a]	Number (%) of patients			
	Gefitinib (N=607)		Carboplatin/Paclitaxel (N=589)	
Time on treatment (n [%])				
>0 months	607	(100.0)	589	(100.0)
>1 month	552	(90.9)	543	(92.2)
>2 months	443	(73.0)	473	(80.3)
>3 months	387	(63.8)	381	(64.7)
>6 months	289	(47.6)	0	
>9 months	174	(28.7)	0	
>12 months	85	(14.0)	0	
Summary of time on treatment (months)				
Mean	6.4		3.4	
Median	5.6		4.1	
Range	0.1 to 22.8		0.7 to 5.9	

Data from Table 35 in the IPASS CSR.
[a] Duration of treatment calculated as date of last dose minus date of first dose plus 1 day for gefitinib and plus 21 days for carboplatin/paclitaxel, to account for the different treatment regimens.
EFS: Evaluable-for-safety; N: Number of patients

Review of overall adverse events in the IPASS study revealed that the majority of patients experienced one or more adverse events during the course of the study as indicated in Table 5. Fewer CTC grade III or IV adverse events (28.7% vs 61%) adverse events leading to discontinuation from treatment (6.9% vs 13.6%) and treatment related adverse events (88.6% vs 96.6%) were reported with gefitinib compared with carboplatin/paclitaxel. The frequency of serious adverse events (16.3% vs 15.6%) and serious adverse events with an outcome of death (3.8% vs 2.7%) were similar for both treatments.

Table 5 Number (%) of patients who had an adverse event in any category (IPASS; EFS population)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]	
	Gefitinib (N=607)	Carboplatin/Paclitaxel (N=589)
	Overall[b]	Overall[b]
Any AE	580 (95.6)	578 (98.1)
Treatment related[c] AE	538 (88.6)	569 (96.6)
Any SAE	99 (16.3)	92 (15.6)
Treatment related[c] SAE	21 (3.5)	53 (9.0)
Non-fatal SAE	79 (13.0)	80 (13.6)
Non-fatal treatment related[c] SAE	17 (2.8)	51 (8.7)
Any AE leading to discontinuation from first-line treatment	42 (6.9)	80[d] (13.6)
Due to treatment related[c] AE	24 (4.0)	67 (11.4)
Due to SAE	25 (4.1)	23 (3.9)
Due to treatment related[c] SAE	9 (1.5)	12 (2.0)
Any AE with outcome death	23 (3.8)	16 (2.7)
Treatment related[c] AE with outcome death	4 (0.7)	3 (0.5)
Any CTC Grade 3 or 4 AE	174 (28.7)	359 (61.0)
Treatment related[c] Grade 3 or 4 AE	99 (16.3)	333 (56.5)
Any CTC Grade 3, 4 or 5 AE	192 (31.6)	368 (62.5)
Treatment related[c] Grade 3, 4 or 5 AE	103 (17.0)	334 (56.7)

Data from Table 37 of the IPASS CSR.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Overall includes all adverse events that occurred whilst receiving first-line treatment or within 28 days after discontinuation.

[c] Treatment related refers to the randomised first-line treatment and not subsequent treatments.

[d] An additional 3 patients (E1414004, E1414007, E1426015) had adverse events leading to discontinuation in the post –treatment period.

AE: adverse event; CTC: Common Terminology Criteria; EFS: Evaluable-for-safety; N: Number of patients; SAE: serious adverse event

In general for the sub-groups of gefitinib-treated patients with positive, negative or unknown EGFR mutation status, the categories for adverse events occurred with similar incidence and were consistent with that observed in the overall gefitinib-treated population with fewer CTC grade III or IV adverse events, adverse events leading to discontinuation and treatment-related adverse events compared with chemotherapy-treated patients. Review of the most common adverse events are summarised in Table 6 and grouped terms of special interest are summarised in Table 7. Events with at least a 10% incidence in either treatment with >3% difference in incidence between treatments are presented in Figure 8.

Table 6 **Most common adverse events (those occurring in at least 10% of patients in either treatment group) or adverse events with a difference in incidence of >5% between treatment groups (IPASS; EFS population)**

System organ class and preferred term	Number (%) of patients[a]	
	Gefitinib (N=607)	Carboplatin/ Paclitaxel (N=589)
	Overall[b]	Overall[b]
Blood and lymphatic disorders[c]		
Anaemia	43 (7.1)	150 (25.5)
Neutropenia	15 (2.5)	223 (37.9)
Leukopenia	13 (2.1)	146 (24.8)
Thrombocytopenia	8 (1.3)	71 (12.1)
Gastrointestinal disorders		
Diarrhoea	283 (46.6)	128 (21.7)
Nausea	101 (16.6)	261 (44.3)
Stomatitis	81 (13.3)	42 (7.1)
Vomiting	78 (12.9)	196 (33.3)
Constipation	73 (12.0)	173 (29.4)
General disorders and administration site conditions		
Fatigue	87 (14.3)	219 (37.2)
Pyrexia	54 (8.9)	61 (10.4)
Infections and Infestations		
Paronychia	82 (13.5)	0 0
Investigations		
ALT increased	64 (10.5)	31 (5.3)
AST increased	53 (8.7)	19 (3.2)
White blood cell count decreased	5 (0.8)	52 (8.8)
Neutrophil count decreased	0 0	40 (6.8)
Metabolism and nutrition disorders		
Anorexia	117 (19.3)	235 (39.9)
Musculoskeletal and connective tissue disorders		
Myalgia	47 (7.7)	186 (31.6)
Arthralgia	39 (6.4)	113 (19.2)
Nervous system disorders		
Peripheral sensory neuropathy	23 (3.8)	141 (23.9)
Hypoaesthesia	21 (3.5)	154 (26.1)
Neuropathy peripheral	9 (1.5)	97 (16.5)
Psychiatric disorders		
Insomnia	88 (14.5)	108 (18.3)
Respiratory, thoracic and mediastinal disorders		
Cough	57 (9.4)	62 (10.5)
Skin and subcutaneous tissue disorders		
Rash	313 (51.6)	120 (20.4)
Dry skin	145 (23.9)	17 (2.9)
Pruritus	107 (17.6)	71 (12.1)
Alopecia	67 (11.0)	344 (58.4)
Acne	66 (10.9)	4 (0.7)
Dermatitis acneiform	35 (5.8)	2 (0.3)

Data from Table 38 of the IPASS CSR.

[a] Percentages are of total patients in each treatment group presented by decreasing order of incidence in the gefitinib group within the System Organ Class. Patients are counted once within any preferred term.

[b] Overall includes all adverse events that occurred whilst receiving first-line treatment or within 28 days after discontinuation.

[c] Clinically significant laboratory findings were only reported as adverse events if a criterion for a serious adverse event was fulfilled: the abnormality caused study treatment to be discontinued, or the investigator insisted the abnormality was to be reported as an adverse event. Therefore, laboratory findings worsening from baseline to CTC grade 3 or 4 should be referred to for the primary assessment of haematological and liver function toxicity. Summary data and discussion is provided in Section 3.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; EFS: Evaluable-for-safety; N: Number of patients

Table 7 Specific adverse events of interest – grouped terms: IPASS (EFS population)

Grouped events	Preferred terms	Number (%) of patients[a] Gefitinib (N=607)	Carboplatin/ paclitaxel (N=589)
Anorexia	anorexia, decreased appetite, oral intake reduced	133 (21.9)	251 (42.6)
Asthenic conditions	asthenia, fatigue, malaise	102 (16.8)	259 (44.0)
Dry eye	dry eye, keratoconjunctivitis sicca	23 (3.8)	1 (0.2)
ILD-type events[b]	acute respiratory distress syndrome, ILD, pneumonitis, radiation pneumonitis	16 (2.6)	8 (1.4)
Lower respiratory tract and lung infections	bronchitis, bronchopneumonia, lower respiratory tract infection, lung infection, pneumonia, pyothorax	38 (6.3)	33 (5.6)
Nail and nail bed conditions	ingrowing nail, koilonychias, nail bed bleeding, nail bed inflammation, nail bed tenderness, nail discolouration, nail disorder, nail pigmentation, nail pitting, onychalgia, onychoclasis, onycholysis, onychomadesis	37 (6.1)	4 (0.7)
Neurotoxicity[c]	dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuropathy peripheral, neurotoxicity, paraesthesia, paraesthesia oral, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy	66 (10.9)	412 (69.9)
Pruritus	pruritus, pruritus allergic, pruritus generalised, rash pruritic	118 (19.4)	74 (12.6)
Rashes/Acnes[d]	HLT 'rashes, eruptions and exanthems', HLT 'acnes' and preferred terms rash pustular, dermatitis, exfoliative rash, rash erythematous, rash follicular, rash papular	402 (66.2)	132 (22.4)
Stomatitis[e]	aphthous stomatitis, mouth ulceration, stomatitis	103 (17.0)	51 (8.7)

Data from Table 39 of the IPASS CSR.

[a] Percentages are of total patients in each treatment group. Patients with events in more than one category are counted once in each of those categories.

[b] The following terms were also searched for but were not present in this study: acute interstitial pneumonitis, alveolitis, alveolitis allergic, alveolitis fibrosing, chest x-ray abnormal, cryptogenic organizing pneumonia, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disorder, lung infiltration, lung infiltration malignant, pneumonitis toxoplasmal, obliterative bronchiolitis, pneumonitis chemical, pneumonitis cryptococcal, pneumonitis fume inhalation, pulmonary fibrosis, pulmonary interstitial emphysema syndrome, pulmonary radiation injury not otherwise specified, pulmonary toxicity, radiation alveolitis, radiation fibrosis – lung.

[c] The following terms were also searched for but not present in this study: neuropathy.

[d] The following terms were also searched for but not present in this study: dermatitis exfoliative, rash vesicular.

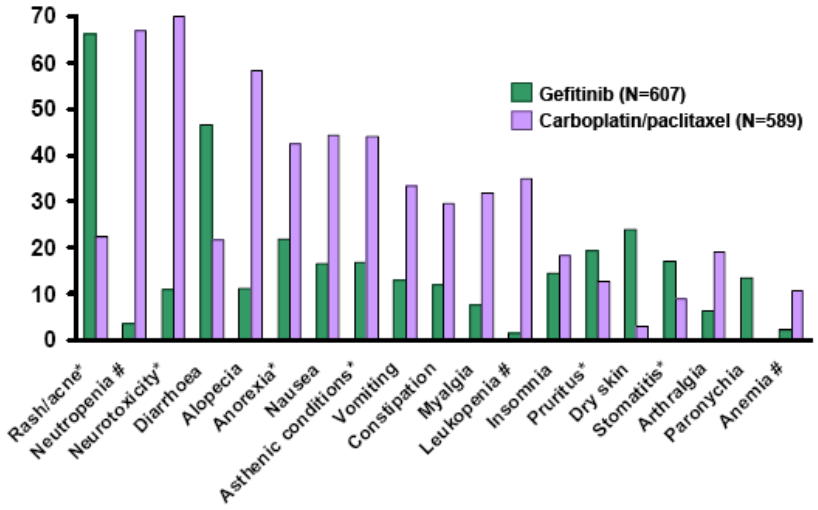
[e] The following terms were also searched for but not present in this study: oral mucosal eruption.

EFS: Evaluable-for-safety; HLT: high level term; ILD: Interstitial lung disease; N: Number of patients

The most common adverse events for gefitinib were rashes, acnes, diarrhoea, dry skin, stomatitis, pruritus, paronychia and increase in liver enzyme alanine transaminase (ALT). In addition increase in the enzyme aspartate transaminase (AST) and nail and nail bed conditions were reported more commonly with gefitinib than chemotherapy. These adverse events are well recognised as part of safety profile of gefitinib.

Figure 8: Most common adverse events (≥10% of patients on either treatment) with >3% difference between treatments

Figure 1 **Most common adverse events (≥10% of patients on either treatment) with >3% difference between treatments**



#Incidences of absolute neutrophil count, white blood cell count, or haemoglobin worsened from baseline to CTC grade 3 or 4 are based on clinical laboratory data (gefitinib N=599, carboplatin/paclitaxel N=577).
*Grouped term (sum of several preferred terms)

As might be expected the most common adverse events with the chemotherapy arm included neurotoxicity, alopecia, neutropenia, asthenia, nausea, vomiting, myalgia, constipation and arthralgia. These are also consistent with the known safety profile of carboplatin/paclitaxel.

As might be expected the incidence of febrile neutropenia was lower in the gefitinib arm being 0.2% compared with the chemotherapy arm (2.9%).

Review of specific events considered possibly associated with gefitinib or the chemotherapy arm was assessed. This is summarised in Table 8. Events of rashes, acnes, diarrhoea and CTC grade at least 3 liver transaminase elevation is reported as statistically significantly higher incidence on the gefitinib arm, whereas events in neurotoxicity CTC grade III/IV haematological toxicity were reported at a statistically significantly higher incidence in the chemotherapy arm. The incidence of nausea and vomiting was significantly higher in the chemotherapy arm.

A total of 192 patients (31.6%) in the gefitinib arm and 368 patients (62.5%) in the chemotherapy arm were reported with at least one adverse event of CTC grade III/V. There was a lower incidence of these in the gefitinib arm. As might be expected the most common events described in relation to gefitinib were increased liver enzymes and diarrhoea whereas neutropenia and leukopenia were most common with carboplatin/paclitaxel.

Review of treatment-related adverse events confirmed that fewer patients on the gefitinib arm experienced these compared to the chemotherapy arm (88.6% versus 96.6%). Consistent with the known safety profile the most frequently reported treatment-related adverse events for gefitinib were rashes, diarrhoea, dry skin and pruritus. The most common frequently reported treatment-related adverse events for the chemotherapy arm were neurotoxicity, alopecia, nausea, asthenia, vomiting, myalgia, constipation, rashes and haematological side effects.

Table 8 Analysis of specific safety events (IPASS; EFS population)

Event[a]	Gefitinib (N=607)		Carboplatin/ paclitaxel (N=589)		Adjusted p-value[b]
	n	(%)	n	(%)	
Events possibly associated with gefitinib					
Rashes/Acnes	398	(65.6)	132	(22.4)	<0.0001
Diarrhoea	274	(45.1)	128	(21.7)	<0.0001
Nausea	74	(12.2)	260	(44.1)	<0.0001
Vomiting	59	(9.7)	193	(32.8)	<0.0001
Elevated liver transaminases (CTC ≥3)[c]	57	(9.4)	6	(1.0)	<0.0001
Events possibly associated with carboplatin/paclitaxel					
Neurotoxicity	30	(4.9)	411	(69.8)	<0.0001
Neutropenia (CTC ≥3)[c]	4	(0.7)	385	(65.4)	<0.0001
Leukopenia (CTC ≥3)[c]	1	(0.2)	202	(34.3)	<0.0001
Anaemia (CTC ≥3)[c]	11	(1.8)	56	(9.5)	<0.0001
Thrombocytopenia (CTC ≥3)[c]	5	(0.8)	29	(4.9)	0.0001

Data from Table 40 of the IPASS CSR.

[a] Data are derived from adverse events occurring on-treatment and during the 28 day follow-up period, and from laboratory data reported on-treatment. Percentages are of total patients in each treatment group presented in decreasing order of incidence in the gefitinib group for events possibly associated with gefitinib, and in decreasing order of incidence in the carboplatin/paclitaxel group for events possibly associated with carboplatin/paclitaxel.

[b] Calculated using the method of Westfall and Young 1993.

[c] Identified from the laboratory data, as abnormal laboratory results were not to be routinely reported as adverse events.

CTC: Common Terminology Criteria; EFS: Evaluable-for-safety; N: Number of patients

Of the 1217 patients randomised in the trial, 450 (37%) had died by the date of cut-off of the 14 April 2008 of whom 223 (36.7%) were in the gefitinib arm and 227 (38.5%) in the chemotherapy arm. The proportion of deaths related to NSCLC alone was similar for the two treatment arms and the frequency of adverse events leading to death was similar in both treatment arms being 3.8% for gefitinib and 2.7% for chemotherapy.

Only a small proportion of patients in both treatment groups were considered by the investigator to have died as a consequence of adverse events being 1% in each arm.

It is of note that the number of deaths occurring within the first 30 days of initiation of treatment was higher in the gefitinib arm being 19 patients versus 11 patients in the chemotherapy arm. The majority were due to death from progressive malignancy. Two deaths in each treatment arm were reported as adverse events. It is considered the possible reason for the initial disadvantage with gefitinib is due to lack of clinical benefit in patients with no EGFR mutation. It is noteworthy that amongst those who are EGFR mutation-negative over half had progressed by the first scan at six weeks.

There were a small number of patients who had adverse events with an outcome of death with the total being 23 patients for gefitinib and 16 patients for chemotherapy. Of these events that were considered related to lung cancer were 18 patients in the gefitinib arm and 10 patients in the chemotherapy arm. The most frequently reported adverse event with outcome of death was pneumonia in both treatment arms with three patients in the gefitinib arm who died because of interstitial lung disease.

Review of serious adverse events revealed that 99 patients in the gefitinib arm and 92 patients in the chemotherapy arm had at least one serious adverse event recorded. Again these were consistent with the known safety profiles for the treatments. Further details regarding hepatic function abnormalities and interstitial lung disease in relation to gefitinib are discussed below. The incidence of treatment-related serious adverse events was lower in the gefitinib treatment group compared with chemotherapy group being 3.5% versus 9%. Treatment-related serious adverse events for patients treated with gefitinib were primarily events predictable from the known pharmacological action of the drug and its known safety profile.

Fewer adverse events leading to treatment discontinuation were reported for the patients receiving gefitinib (6.9%) compared with chemotherapy (13.6%). The most frequently reported adverse events leading to treatment discontinuation with gefitinib included hepatic dysfunction, pneumonia and interstitial lung disease. The most frequently reported adverse events leading to discontinuation of chemotherapy included neutropenia, thrombocytopenia, drug hypersensitivity and neuropathy.

Review of the incidence of interstitial lung disease (ILD) in relation to gefitinib in the IPASS study revealed that 16 events meeting this criteria occurred in patients receiving gefitinib of whom eight had CTC grade III or greater. Three of the ILD cases in the gefitinib arm and one case of acute respiratory distress syndrome in the chemotherapy arm had an outcome of death. All three of the ILD events in the gefitinib arm were considered treatment-related.

When evaluated by EGFR mutation status there was a slightly higher incidence of ILD type events in the sub-group of EGFR mutation-negative patients compared with the other groups, being 6.6% versus 3.8% and 1.3% for the negative, positive and unknown groups respectively, for patients receiving gefitinib.

This incidence of interstitial lung disease is consistent with that which had been previously reported in relation to gefitinib. This is indicative of a potentially severe side effect which needs to be carefully monitored.

Review of clinical laboratory evaluations including the clinically relevant deteriorations in haematological parameters in the IPASS study indicates that the frequency of these was generally low in relation to gefitinib and it is generally accepted that neutropenia is not associated with gefitinib treatment and that the changes documented were due to the second line chemotherapy.

Review of clinical chemistry parameters in the IPASS study particularly assessed the influence on hepatic function in those patients receiving gefitinib. As expected the incidence of hepatic function abnormalities was higher in the gefitinib treatment arm. Twenty five patients (4.3%) in the gefitinib treatment arm and seven patients (1.2%) in the chemotherapy arm experienced changes in total bilirubin of two or more CTC grades from baseline.

Six patients were identified in the gefitinib-treated arm who had bilirubin increases of at least two above normal and four had also increases in other liver enzymes. No hepatic adverse events were reported for these patients as they were asymptomatic. The sponsors have reviewed these events and corresponding clinical status in these patients and considered that the laboratory abnormalities were not indicative of drug-induced hepatitis with gefitinib and that the events were due to other factors. The hepatic laboratory abnormalities observed did not lead to clinically significant liver disorders in this study.

There were no other significant changes in other chemical parameters in the IPASS study. A small number of creatinine changes were observed of whom seven were gefitinib-treated patients and three chemotherapy patients. None of these were considered

clinically significant and some doubt was raised regarding any causative association with gefitinib.

No changes in vital signs were considered clinically meaningful in relation to either arm of study in the IPASS trial.

Supporting studies

In the Phase II trial INSTEP, of the 201 patients who received at least one dose of study treatment, 100 patients and 101 patients were treated with gefitinib or placebo respectively and at the time of data cut-off (22 February 2007), median exposure to the two treatments was similar at approximately 1.5 months.

For the INVITE study, of the 190 patients who received at least one dose of study treatment (94 and 96 patients in the gefitinib and vinorelbine arms respectively at the time of data cut-off of 24 February 2006), median exposure to gefitinib was 77 days while just under half the patients on vinorelbine had received vinorelbine for at least four cycles.

With regard to the incidence of adverse events in the other studies, limited safety data available from study JP0056 reports statistically significant differences for gefitinib versus the chemotherapy arm respectively in the incidence of some adverse events including grade IV neutropenia (33% for chemotherapy vs 1% for gefitinib), while grade III/IV liver dysfunction was 25% for gefitinib versus 1% for chemotherapy and grade III neuropathy was 5% for chemotherapy versus 0% for gefitinib.

Limited safety data was available from study 0054 in which gefitinib is compared with the alternative doublet gemcitabine/cisplatin. It was documented that there was no unusual toxicity in either treatment arm with CTC grade III or IV toxicity significantly less common than the gefitinib arm being 28.3% versus 67.3%, $p<0.0001$.

In INSTEP the majority of patients (approximately 93% in both treatment arms) experienced one or more adverse events. There were no clinically relevant differences between the treatment groups; the frequency of serious adverse events for gefitinib versus placebo was 25% and 24.8%, respectively, and for CTC grade III/IV adverse events it was 36% and 42.6% of patients, respectively. The frequency of adverse events leading to discontinuation of therapy was 14% versus 6.9% and adverse events with an outcome of death was 10% versus 3% of patients, which was slightly higher in the gefitinib-treated patients. As might be expected there were more gefitinib patients who experienced adverse events that were considered by the investigator to be treatment-related (63% vs 35.6%). The most frequently reported adverse events in association with gefitinib were diarrhoea and skin disorders, with the majority being grade I or II.

In the INVITE study the majority of patients experienced at least one adverse event in the course of the study; the overall incidence being 83% for gefitinib versus 89.6% for vinorelbine. There was no clinically relevant difference between the two treatment groups with the frequency of serious adverse events being 31.9% and 32.3%, respectively; and for adverse events with the outcome of death being 8.5% and 10.4%, respectively. Fewer patients taking gefitinib reported grade III or IV adverse events (37.2% vs 53.1%) or discontinued study treatment due to adverse events (12.8% vs 21.9%). Fewer patients taking gefitinib reported treatment-related adverse events (57.4% vs 75%).

Review of deaths revealed that of the 201 patients in the INSTEP trial, 169 patients had died by the date of cut-off with 84% of patients receiving gefitinib deceased and 84.2% for those receiving placebo. Ten patients had an adverse event with an outcome of death in the gefitinib group (10%) compared with 3% for placebo. The number of patients who died as a consequence of an adverse event alone was five in the gefitinib arm and one in the placebo arm. There were no trends relating to specific adverse events with a fatal outcome and no specific event was reported for more than one patient. None of the

adverse events leading to death was considered by the investigator to be causally related to treatment.

In the INVITE study 99 patients had died by the date of cut-off including 52.1% of patients receiving gefitinib and 52.1% of patients receiving vinorelbine. The number of deaths as a result of an adverse event in the gefitinib arm was eight compared to ten for vinorelbine. There were no apparent trends relating to specific adverse events with a fatal outcome. Adverse events leading to death were considered by the investigator to be causally related to study treatment in three patients taking vinorelbine but none taking gefitinib.

Review of serious adverse events in the INSTEP study revealed that there was similar frequency of these in both treatment groups being 25 and 24 patients in each group. There were no clinically relevant differences in the incidences of individual serious adverse events between the treatment groups. Four serious adverse events were considered by the investigator to be related to study treatment in the gefitinib group versus one in the placebo group.

In the INVITE study the frequency of serious adverse events were similar for the two treatment arms being 30 and 31 patients in each arm for gefitinib and vinorelbine, respectively. The types of serious adverse events reported were consistent with the known toxicity profile of the two arms of treatment. There were 17 serious adverse events considered to be related to treatment by the investigator in the vinorelbine group versus three in the gefitinib group. Those associated with the use of gefitinib were ILD in one case and diarrhoea and rash in two others.

Review of treatment discontinuations revealed that in the INSTEP study a total of 21 patients discontinued therapy with the incidence higher for gefitinib being 14 versus 7 for placebo. The majority of adverse events leading to discontinuation were gastrointestinal disorders such as diarrhoea. Only six of these adverse events leading to treatment discontinuation were considered to be directly related to gefitinib by the investigator compared to three in the placebo group.

In the INVITE study the frequency of discontinuation due to adverse events was lower in the gefitinib group being 12 compared to 21 for vinorelbine. The incidence of specific adverse events leading to discontinuation was low for both treatment groups. Thirteen patients in the vinorelbine group discontinued due to adverse events considered by the investigator to be related to the study treatment compared to five receiving gefitinib.

Review of clinical laboratory data from the INSTEP and INVITE studies revealed that in INSTEP the majority of patients experienced no changes from baseline in haematological parameters in either arm of study. In the INVITE study, consistent with the known safety profile of vinorelbine, a significantly greater number of patients experienced haematological abnormalities, particularly neutropenia, with an incidence of 43.5%. There were no obvious changes in haematological parameters in relation to gefitinib.

In relation to hepatic parameters in INSTEP, the majority of transaminase changes noted were mild to moderate with no clinically significant differences observed between the two treatment groups. In INVITE a greater proportion of the patients in the gefitinib group experienced deterioration in CTC grade II or more from baseline of liver enzymes compared with the vinorelbine. One patient had a grade III elevation of AST and four patients had a grade III elevation of ALT and one patient had a grade IV ALT elevation.

Evaluator's comment

The safety data from the pivotal trial IPASS and the supporting studies (principally INSTEP and INVITE) essentially document that which is well characterised in relation to gefitinib therapy in earlier trials and clinical usage. Gastrointestinal symptoms (predominantly diarrhoea) and skin irritations appear to be most common and certainly well previously

documented. There is no real additional data from these studies over and above that which have already been well established. Of note is the definite concern regarding an incidence of hepatic dysfunction and interstitial lung disease (ILD). These represent potentially serious adverse events that require careful monitoring. The incidence of these has been previously well documented but nevertheless confirmation of these from the present studies determines the requirement for appropriate labelling and careful clinical monitoring. Nevertheless the overall safety profile for gefitinib from these studies is essentially in line with that well documented and therefore does not preclude consideration of gefitinib for approval for the current indication.

Previous evaluation

Although not evaluated in this submission, the proposal to modify the second line indication relies on the INTEREST and three other trials which were evaluated in the previous submission. For completeness, a summary of the safety of these trials is provided.

The four trials provided safety data. Safety in previously evaluated trials was also considered, so that the total database was 2,200 patients. Safety in the new trials was consistent with previous experience. The overall incidence of adverse reactions and the incidence of serious reactions were lower with Iressa (72%) than docetaxel (82%). In the pivotal INTEREST trial, 72% of Iressa patients experienced an adverse reaction compared with 82% of docetaxel patients and, for serious reactions, 4% versus 18% respectively. Common adverse events significantly more frequent with Iressa were rash (49%) and diarrhoea (35%) and with docetaxel, neutropenia (74%), asthenia (48%) and alopecia (36%).6

The incidence of ILD, a reaction of interest, was higher for Iressa (0.5%) than docetaxel (0.1%) in the INTEREST trial. One patient on Iressa (0.1%) died due to ILD compared with none on docetaxel. In the Japanese V-15-32 trial, ILD occurred in 6% of Iressa patients and 4% of docetaxel patients. There were 3 deaths due to ILD (1.2%) with Iressa but none with docetaxel. In the SIGN trial, there were no instances of ILD with Iressa but 2 (3%) with docetaxel. In the Korean ISTANA trial, ILD incidence was similar for Iressa and docetaxel – 3 patients each (4%).

Post-marketing data

Gefitinib in a dose of 250 mg/day as monotherapy for the treatment of non small-cell lung cancer is currently approved in 36 countries. Estimated exposure to gefitinib as of March 2009 is >300,000 patients. Approximately 6% of these patients were enrolled in clinical trials while a further 19% received gefitinib in expanded access programmes and the remaining 75% received gefitinib via marketed use.

In the period from July 2002 to the 31 March 2009, a total of 13,527 adverse events had been reported. Of these 4,842 reported serious adverse events. The overall safety profile generated from these reports was generally consistent with that seen in the gefitinib 250 mg monotherapy NSCLC clinical trials. Safety signals have been raised from post-marketing adverse events including recognition of an incidence of ILD, pancreatitis, allergic reactions including angioedema and urticaria, hepatitis and pyrexia. These adverse events have been appropriately documented and placed in the relevant product information literature.

Clinical summary and conclusions

The principal focus of this evaluation was the pivotal trial IPASS, which was a Phase III randomised study conducted in Asia which compared once daily oral gefitinib 250 mg monotherapy with carboplatin/paclitaxel doublet chemotherapy in 1217 clinically selected first line non small-cell lung cancer patients with adenocarcinoma histology who were ex-light smokers or never-smokers. The study set out to demonstrate non-inferiority of gefitinib relative to the intravenous doublet chemotherapy in terms of PFS and improved tolerability. The secondary objectives also included determination of OS, objective tumour response rate and quality of life measures. The exploratory objectives related to assessment of baseline biomarker data in the context of determining potential differences with respect to PFS and the secondary objectives.

The efficacy findings demonstrated superiority of gefitinib relative to carboplatin/paclitaxel in terms of PFS in the overall population with an HR of 0.74 ($p<0.0001$). It is noteworthy the HR was not constant over time with a probability of being progression free in favour of the chemotherapy doublet in the first six months and in favour of gefitinib in the following 15 months of follow up. This was likely to be because of the different effect of gefitinib in sub-groups defined by EGFR mutation status.

In addition gefitinib demonstrated superior objective response rate and a higher rate of clinically important improvements in quality of life and the doublet chemotherapy with similar overall survival and symptom improvement rates. OS was similar for both treatments based on data available at the data cut-off for the primary analysis of PFS although follow up is ongoing.

The relative efficacy of the primary variable (PFS) and the secondary variables (response rate, OS and quality of life data) depended on epidermal growth factor receptor (EGFR) mutation status with overall population results being driven by differential outcomes for EGFR mutation-positive versus EGFR mutation-negative sub-groups (treatment by mutation status interaction test, $p<0.0001$). Pre-planned analysis of the primary endpoint showed that PFS was significantly longer for gefitinib than the doublet chemotherapy in EGFR mutation-positive patients, median 9.5 months versus 6 months with an HR of 0.48, $p<0.0001$, and significantly longer for carboplatin/paclitaxel than gefitinib in patients who are EGFR mutation-negative with a median of 5.5 months versus 1.5 months and an HR 2.85 ($p<0.0001$). Within these sub-groups the HR appeared to be constant over time and Kaplan-Meier curves did not cross. In patients with unknown mutation status, PFS results (HR 0.68, $p<0.0001$) were similar to that of the overall population.

In EGFR mutation-positive patients, PFS was significantly longer for gefitinib than doublet chemotherapy and overall response rate was superior for gefitinib versus chemotherapy and significantly more gefitinib-treated patients experienced an improvement in quality of life and lung cancer symptoms versus chemotherapy. Conversely, in EGFR mutation-negative patients, PFS was significantly longer for chemotherapy than gefitinib and the response rate was superior for chemotherapy and significantly more chemotherapy patients experienced an improvement in quality of life and lung cancer symptoms versus gefitinib.

Two independently run Phase III studies of gefitinib versus doublet chemotherapy in systemically untreated NSCLC patients were also included in this submission (study JP0056 and study 0054). Study JP0056 compared gefitinib with carboplatin/paclitaxel in a prospective study of all EGFR mutation-positive patients including patients irrespective of histological or smoking status, while study 0054 provides data from a comparison of gefitinib with gemcitabine/cisplatin in never-smokers with adenocarcinoma histology and included assessment of differential efficacy for sub-groups defined by EGFR mutation status.

These two supplementary trials revealed numerically improved PFS outcomes for EGFR mutation-positive patients treated with gefitinib compared to those treated with doublet chemotherapy in both studies indicating efficacy of gefitinib in EGFR mutation-positive first line patients is consistent across these trials. It is worth noting that the trial JP0056 was a prospective study in EGFR mutation-positive patients which included patients irrespective of histological or smoking status.

Two additional Phase II trials were provided in this submission, namely studies INSTEP and INVITE. These studies compared gefitinib with placebo (INSTEP) in patients with poor performance status while INVITE compared gefitinib with vinorelbine in elderly patients. Both studies demonstrated similarities for gefitinib versus the comparator arm. Nevertheless the number of patients involved in the two trials is relatively small and EGFR mutation status was not assessed routinely. These studies therefore provide very limited data in terms of potential support for the proposed indication.

Review of safety for the IPASS study involved 607 patients who are exposed to gefitinib. The most commonly reported adverse events for patients receiving gefitinib were diarrhoea and skin reactions. Approximately 32% of the gefitinib-treated patients had severe adverse events and 7% of gefitinib-treated patients stopped therapy due to an adverse event. In patients with EGFR mutation-positive status the safety profile of gefitinib was consistent with the profile for the overall gefitinib-treated population and consistent with the known safety profile of gefitinib. It is worth noting that in the IPASS study there were incidences of interstitial lung disease, which clearly indicates a potentially serious adverse effect. Furthermore there was also further evidence to support the potential for gefitinib to influence hepatic function resulting in transaminase elevation and potentially clinically significant hepatic dysfunction. Both of these adverse events are well documented in the past and appropriately placed in the Product Information literature with relevant requirement for careful monitoring.

There was little in the way of worthwhile safety data available from either studies JP0056 or 0054. The data from the Phase II trials INSTEP and INVITE were essentially comparable to that reported in the IPASS study, again confirming the known safety profile for gefitinib.

The pivotal trial IPASS is a large trial involving in excess of 1200 patients, appropriately randomised to gefitinib and doublet chemotherapy in an Asian population with adequate numbers to assess EGFR mutation status and comparison between the EGFR mutation-positive and -negative patients. The results are robust and clearly indicate a benefit for the EGFR mutation-positive patients in terms of PFS, response rate and quality of life. The data regarding OS will require prolonged follow up to adequately determine possible benefits in relation to these criteria. The two independent Phase III trials also support the role of gefitinib in the EGFR mutation-positive patients. The data provided in this submission from these two independent studies is brief, but nevertheless reinforces the fact that gefitinib is a worthwhile approach in the management of patients with advanced stage NSCLC who are EGFR mutation-positive. This is biologically sensible and therefore represents an advance in the potential management of patients with lung cancer. The safety profile demonstrated in the IPASS study is consistent with that generally well recognised for gefitinib.

Accordingly the evaluator considered that it was appropriate to recommend approval for gefitinib for the proposed new indication namely gefitinib for the first line treatment of patients with locally advanced or metastatic NSCLC who have activating mutations of EGFR tyrosine kinase.

V. Pharmacovigilance findings

Risk management plan

A Risk Management Plan (RMP) was submitted by AstraZeneca Pty Ltd in support of the application, and the following important safety concerns were identified by the sponsor:

Important identified risks	Interstitial lung disease Hepatitis
Important potential risks	Haemorrhage Gastrointestinal haemorrhage Tumour haemorrhage Leukaemia-type events Cerebrovascular events Drug interactions: oral anticoagulants, CYP3A4 inducers and inhibitors, CYP2D6, and drugs that cause significant sustained elevations in gastric pH.
Important missing information	Pregnant or lactating women Severe renal impairment

The RMP was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM) and it was considered that the RMP was acceptable and the proposed application of routine and additional pharmacovigilance activities to the safety concerns as identified by the sponsor was also acceptable.

Nevertheless the targeted follow-up questionnaires for the specified safety concerns do not appear to have been provided. Therefore it was requested that the sponsor provide copies of these questionnaires for each specified safety concern to the TGA.

In regard to the completed or ongoing studies, they are not considered as being part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocols have not been reviewed.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in an application of this type.

Clinical

New Indication

Efficacy

In a randomised, open-label, parallel-group trial (IPASS) in patients with advanced adenocarcinoma NSCLC who had not previously received chemotherapy,3 Iressa orally 250 mg daily significantly increased progression free survival (PFS) (the primary endpoint), overall response rate and FACT-L quality of life, but not LCS score for disease-related symptoms, compared with intravenous carboplatin AUC 5 or 6 mg/mL/min and paclitaxel 200 mg/m^2 every 3 weeks, a standard treatment[13] (Table 9). The Hazard Ratio (HR) for PFS was not constant over time, the survival curves crossing around the median (Figure 2). The survival curves for overall survival (OS) also crossed. The difference in OS was not statistically or clinically significant.

The majority of subjects were female (79%) and median age was 57 (range 24-84) years. Patients were former light or never smokers – the majority never smoked (94%). Iressa or carboplatin/paclitaxel was given until disease progression or unacceptable toxicity however carboplatin/paclitaxel was given for a maximum six cycles. The median duration of treatment with Iressa was 5.6 (range 0-23) months and with carboplatin/paclitaxel it was 4.1 (range 1-6) months. The trial was conducted in Asia – 99% of subjects were Oriental.

The benefits of Iressa over carboplatin/paclitaxel were enhanced in subjects with EGFR mutations but significantly worse than carboplatin/paclitaxel in those without mutations (Tables 10 and 11) which explains the crossing of the survival curves in the overall analysis. In subjects with EGFR mutations, Iressa increased PFS by a median of 3.2 months. There was a trend to increased OS which is likely to be confounded by post-progression treatment.

Table 9: IPASS Trial – Efficacy Results – *Overall – Intent-to-Treat*

	Iressa po 250 mg daily n=609	**Carbo/Pacli iv q3w n=608**	**Hazard Ratio[1] or Difference [95% CI]**
Progression-Free Survival median *mths*	5.7	5.8	0.74 [0.65, 0.85]
Overall Survival median *mths*	18.6	17.3	0.91 [0.76, 1.10]
Overall Response Rate[2] *%*	43.0	32.2	10.8 [5.4, 16.2]
Quality-of-Life Improved[3] *%*	**n=590**	**n=561**	
FACT-L	48.0	40.8	7.1 [1.4, 12.9]
LCS	51.5	48.5	3.0 [-2.7, 8.8]

[13] *Cancer Institute NSW:* https://www.eviq.org.au/Category/tabid/65/categoryid/322/Default.aspx.

[1] Cox proportional hazards model estimate for Iressa/carbo-pacli adjusted for WHO performance status, smoking history and gender. [2] RECIST criteria. [3] ≥ 6-point increase in FACT-L and TOI and ≥ 2-point increase in LCS maintained for ≥ 21 days. FACT-L: Functional Assessment of Cancer Therapy - Lung, LCS: Lung Cancer Subscale.

Table 10: IPASS Trial – Efficacy Results – *EGFR Mutation-positive – Intent-to-Treat*

	Iressa po 250 mg daily n=132	**Carbo/Pacli iv q3w n=129**	**Hazard Ratio[1] or Difference [95% CI]**
Progression-Free Survival median *mths*	9.5	6.3	0.48 [0.36, 0.64]
Overall Survival median *mths*	NR	19.5	0.78 [0.50, 1.20]
Overall Response Rate[2] %	71.2	47.3	23.9 [12.4, 35.5]
Quality-of-Life Improved[3] *%*	**n=131**	**n=128**	
FACT-L	70.2	44.5	25.7 [14.1, 37.3]
LCS	75.6	53.9	21.7 [10.3, 33.0]

[1] Cox proportional hazards model estimate for Iressa/carbo-pacli adjusted for WHO performance status, smoking history and gender. [2] RECIST criteria. [3] ≥ 6-point increase in FACT-L and TOI and ≥ 2-point increase in LCS maintained for ≥ 21 days. FACT-L: Functional Assessment of Cancer Therapy - Lung, LCS: Lung Cancer Subscale. NR: Not Reached.

Table 11: IPASS Trial – Efficacy Results – EGFR Mutation-negative – Intent-to-Treat

	Iressa po 250 mg daily n=91	Carbo/Pacli iv q3w n=85	Hazard Ratio[1] or Difference [95% CI]
Progression-Free Survival median *mths*	1.5	5.5	2.85 [2.05, 3.98]
Overall Survival median *mths*	12.1	12.6	1.38 [0.92, 2.09]
Overall Response Rate[2] %	1.1	23.5	-22.4 [-31.7, -13.2]
Quality-of-Life Improved[3] *%*	**n=89**	**n=80**	
FACT-L	14.6	36.3	-21.6 [-34.5, -8.8]
LCS	20.2	47.5	-27.3 [-41.0, -13.5]

[1] Cox proportional hazards model estimate for Iressa/carbo-pacli adjusted for WHO performance status, smoking history and gender. [2] RECIST criteria. [3] ≥ 6-point increase in FACT-L and TOI and ≥ 2-point increase in LCS maintained for ≥ 21 days. FACT-L: Functional Assessment of Cancer Therapy - Lung, LCS: Lung Cancer Subscale.

Trials JP0056 and 0054, reported in summary form, were supportive of the efficacy of Iressa in subjects with advanced NSCLC with EGFR mutations who had not previously received chemotherapy. Trial JP0056 involved general NSCLC subjects (n=200) and trial 0054 involved subjects with adenocarcinoma (n=309). Trial JP0056 involved subjects with EGFR mutations exclusively. Two other trials, INSTEP (n=201) and INVITE (n=196), both in general NSCLC subjects, had insufficient data on EGFR mutation status to draw conclusions.

Safety

The major safety data were from the pivotal IPASS trial. The incidence of severe adverse events and adverse events leading to treatment discontinuation were lower with Iressa than with carboplatin/paclitaxel (29% vs 61% for severe and 7% vs 14% for discontinuations). However, the incidences of serious adverse events and adverse events leading to deaths were similar between the treatment groups (16% vs 16% for serious and 4% vs 3% for deaths). Patients treated with Iressa had a higher incidence of mortality in the first 30 days of treatment which may be due to lack of clinical benefit in subjects without EGFR mutations. The incidence of deaths in Iressa-treated subjects without EGFR mutations was 5.5% and in those with mutations 0.8%. The majority of deaths were due to disease progression.

Common treatment-related adverse events with Iressa were rash, diarrhoea, dry skin and pruritus. Serious events were hepatic dysfunction, pneumonia and interstitial lung disease (ILD). The adverse event profile of Iressa in subjects with EGFR mutations was similar to

the profile in the overall population. The adverse event profile was consistent with the known profile for Iressa.

The safety data from the other studies including the study in subjects with EGFR mutations was also consistent with the known safety profile of Iressa.

Modified Indication - Pre-treated NSCLC

No new data were submitted but data from the previous submission were considered.

Risk management plan

The RMP was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM) and it was considered that the RMP was acceptable and the proposed application of routine and additional pharmacovigilance activities to the safety concerns as identified by the sponsor was also acceptable.

A small number of amendments to the RMP and the proposed PI were recommended.

Risk-benefit analysis

In the new indication (first line NSCLC), Iressa significantly increased PFS but not OS compared with a standard regimen, carboplatin/paclitaxel, in patients with advanced adenocarcinoma NSCLC (IPASS trial). The survival curves crossed. Subgroup analysis by EGFR mutation status showed that the benefit of Iressa was confined to subjects with EGFR mutations. The evaluator recommended approval of the new indication.

The trial population had adenocarcinoma of the lung rather than the more general NSCLC. The trial population was also almost exclusively Asian. The results are likely to be valid in a general NSCLC population based on the supportive trial JP0056 and the INTEREST and ISEL trials in pre-treated NSCLC (see below).

In the modified indication (pre-treated NSCLC), the sponsor has not addressed the ADEC reasons for rejection of their previous application. It is claimed in their *Clinical Overview* that, in the second line INTEREST trial, there were no clinically relevant differences between Iressa and docetaxel in any subgroup.

The TGA believe that the data from the INTEREST trial and a previous second line trial ISEL suggest that the benefits of Iressa are limited to patients with EGFR mutations (Tables 12 and 13).

Despite the few subjects with EGFR mutation data, there are clear trends in favour of Iressa in subjects with EGFR mutations whilst Iressa had minimal effects in subjects without mutations (worse than the control group in the INTEREST trial). This is particularly apparent for PFS, time to treatment failure (TTF) and overall response rate (ORR). Results for OS are likely to be confounded by post-progression treatment. These data combined with the IPASS data in first line patients supports restricts the indication in pre-treated NSCLC to patients with EGFR mutations.

Table 12: INTEREST Trial – Efficacy Results – "*Evaluable for Efficacy*"[6]

	Iressa po 250 mg daily	Docetaxel iv q3w	Hazard Ratio[1] or Difference [95% CI]
OS median *mths*			
All Subjects	7.6 (n=723)	8.0 (n=710)	1.02 [0.91, 1.15]
Mutation-Positive	14.2 (n=22)	16.6 (n=22)	0.83 [0.41, 1.67]
Mutation-Negative	6.4 (n=119)	6.0 (n=134)	1.02 [0.78, 1.33]
PFS median *mths*			
All Subjects	2.2 (n=659)	2.7 (n=657)	1.04 [0.93, 1.18]
Mutation-Positive	7.0 (n=19)	4.1 (n=19)	0.16 [0.05, 0.49]
Mutation-Negative	1.7 (n=106)	2.6 (n=123)	1.24 [0.94, 1.64]
ORR[2] *%*			
All Subjects	9.1 (n=659)	7.6 (n=657)	1.5 [-1.5, 4.5]
Mutation-Positive	42.1 (n=19)	21.1 (n=19)	21.0 [-8.2, 46.0]
Mutation-Negative	6.6 (n=106)	9.8 (n=123)	-3.2 [-10.5, 4.4]

[1] Cox proportional hazards model estimate of Iressa/docetaxel for PFS and OS and difference Iressa – docetaxel for ORR. [2] RECIST criteria. PFS: Progression-Free Survival, OS: Overall Survival, ORR: Overall Response Rate.

Table 13: ISEL Trial – Efficacy Results – Intent-to-Treat for OS, TTF and "Evaluable" for ORR[14]

	Iressa po 250 mg daily	Placebo	Hazard Ratio[1] or Difference [95% CI]
OS median *mths*			
All Subjects	5.6 (n=1129)	5.1 (n=563)	0.89 [0.77, 1.02]
Mutation-Positive	NR (n=21)	4.3 (n=5)	ND
Mutation-Negative	3.7 (n=132)	5.9 (n=57)	1.16 [0.79, 1.72]
TTF median *mths*			
All Subjects	3.0 (n=1129)	2.6 (n=563)	0.82 [0.73, 0.92]
Mutation-Positive	10.8 (n=21)	3.8 (n=5)	0.79 [0.20, 3.12]
Mutation-Negative	2.0 (n=132)	2.6 (n=57)	1.10 [0.78, 1.56]
ORR[2] %			
All Subjects	8.0 (n=959)	1.3 (n=480)	6.7 [4.7, 8.8]
Mutation-Positive	37.5 (n=16)	0.0 (n=*19)	37.5 [-15.1, 61.4]
Mutation-Negative	2.6 (n=116)	0.0 (n=*123)	2.6 [-5.6, 7.3]

[1] Cox proportional hazards model estimate of Iressa/placebo for TTF and OS and difference Iressa – placebo for ORR. [2] RECIST criteria. TTF: Time to Treatment Failure, OS: Overall Survival, ORR: Overall Response Rate.

ND: Not Done, NR: Not Reached.

It is noteworthy that OS was lower in the ISEL trial than the INTEREST trial. This reflects the more refractory treatment population in the ISEL trial – 90% of subjects had progressed within 90 days of previous chemotherapy compared with 58% in the INTEREST trial. However, despite the greater refractoriness of subjects in the ISEL trial, Iressa still appears to have significant effects in subjects with EGFR mutations.

[14] Hirsch FR, Varella-Garcia M, Bunn PA, et al. Molecular predictors of outcome with gefitinib in a Phase III placebo-controlled study in advanced non-small-cell lung cancer. J Clin Oncol 2006; 24: 5034-5042.

The adverse event profile of Iressa was consistent with previous experience. There did not appear to be specific safety issues with Iressa in subjects with EGFR mutations compared with the general Iressa-treated population.

The Delegate recommended approval of the following indication:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), who have activating mutations of the EGFR tyrosine kinase.

The Delegate recommended that the application to change the current indication (previously-treated patients) be rejected on the grounds that efficacy has not been established in the proposed population. In particular, the indication does not take account of EGFR mutation status.

The sponsor disagreed with this assessment and in its pre-ACPM submission, provided reasons why this part of the application should be accepted.

The sponsor considered that the proposed indication for Iressa in a broad pre-treated NSCLC population is supported by direct evidence of Iressa efficacy compared to other approved agents in the pre-treated setting and has been demonstrated in the following points:

- *In the key Phase III study (INTEREST) of Iressa versus docetaxel:*
  - *Iressa has non-inferior OS, similar PFS and ORR, and superior Quality of Life (QoL) improvement rates compared with docetaxel in an unselected population*
  - *No clinically or statistically relevant disadvantages in efficacy were observed for the EGFR mutation-negative sub-population treated with Iressa in comparison to those treated with docetaxel*
- *Findings from INTEREST are supported by data from additional comparative studies of Iressa versus docetaxel (V-15-32, SIGN and ISTANA) (previously submitted as part of INTEREST submission).*

The Delegate has suggested that in spite of the OS results demonstrated in INTEREST that these results are confounded by crossover and therefore should be discounted. The sponsor contended that post-discontinuation treatment is highly unlikely to have influenced the survival result in favour of Iressa towards non-inferiority as the type of post-discontinuation treatment is balanced between arms and secondary endpoints which are largely unaffected by post-discontinuation treatment are consistent with OS. The crossover in the study represents the standard clinical practice and to conduct the study without crossover would have been unethical. In conclusion, the results of this study should not be discounted.

The Delegate has stated in his overview that Iressa had minimal effects in subjects without mutations, and this is particularly apparent for PFS, TTF and ORR. However, as stated above, the sponsor indicated that no clinically or statistically relevant disadvantages in efficacy were observed for the EGFR mutation-negative sub-population treated with Iressa in comparison to those treated with docetaxel. Further, the conclusion of the INTEREST data as presented in the TGA Clinical Evaluation report stated the following:

"Overall the INTEREST study provided adequate evidence for non-inferiority of gefitinib with that of docetaxel in terms of overall survival. The PFS and ORR were also similar in both treatment groups. Age, gender, smoking status and EGFR-status did not appear to have significant effects in the therapeutic benefits of gefitinib. Furthermore, gefitinib treated patients showed significantly greater improvement in patient reported outcomes of TOI and FACT-L while there was no significant difference in lung cancer symptoms."

Based on the existing data the sponsor did not agree with the Delegate's view that an indication for Iressa in the pre-treated setting should be restricted by EGFR mutation status. In the sponsor's opinion, data demonstrate that Iressa 250 mg offers no significant difference in OS (with non- inferiority proven in the pivotal INTEREST study), a more favourable

safety/tolerability profile, clinically important QoL improvements, and the convenience of a once-daily oral tablet when compared with docetaxel 75 mg/m², a recognised current standard of care, for patients who have received platinum-based chemotherapy. Collectively, INTEREST and the supportive studies (SIGN, V-15-32, and ISTANA) provide confirmatory data in support of a more favourable benefit:risk profile for oral Iressa 250 mg compared with intravenous docetaxel for pre-treated NSCLC patients. In addition, the INTEREST and V-15-32 clinical studies found no strong or credible differentiation in OS between Iressa and docetaxel in any subgroup, therefore this more favourable benefit:risk profile applies to all patient subgroups in the pre-treated setting.

The sponsor contended that the submitted data for the INTEREST study continue to support its proposed use of Iressa in the broad pre-treated NSCLC population where the comparator treatment is singlet chemotherapy. This is a different setting to the first line setting in IPASS where the comparator treatment is a substantially more active doublet chemotherapy regimen, and should therefore be evaluated separately.

The sponsor noted that all approved agents offer limited efficacy in the pre-treated NSCLC setting and that, currently, Iressa is the only EGFR TKI which has shown non-inferior efficacy in a broad pre-treated population versus active chemotherapy comparator. Iressa also has the additional advantages of being a well tolerated oral tablet which has positive impact on patient quality of life.

However, in order to facilitate the conclusion of the submission, the sponsor agreed to accept the imposition of the Delegate's proposed indication for Iressa as follows:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), who have activating mutations of the EGFR tyrosine kinase.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval of the following indication.

For the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), whose tumours express activating mutations of the EGFR TK (tyrosine kinase).

In making this recommendation, the ACPM agreed with the Delegate that the safety and efficacy evidence supported the new indication for Iressa for first line therapy and for previously treated patients only in the context of being limited to patients with mutations of EGFR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Iressa containing gefitinib 250 mg, indicated for:

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase.

Approval was subject to the implementation of the revised Risk Management Plan submitted on 29 June 2010 as agreed with the Office of Medicines Safety Monitoring.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au>.

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