Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Erlotinib

Proprietary Product Name: Tarceva

Sponsor: Roche Products Pty Limited

January 2013

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 of Indications
Decision:	Approved
Date of Decision:	29 June 2012
Active ingredient(s):	Erlotinib
Product Name(s):	Tarceva
Sponsor's Name and Address:	Roche Products Pty Limited PO Box 255, Dee Why NSW 2099
Dose form(s):	Film-coated tablets
Strength(s):	25 mg, 100 mg and 150 mg
Container(s):	Blister pack
Pack size(s):	30's
Approved Therapeutic use:	For the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.[1]
Route(s) of administration:	Oral
Dosage:	150 mg daily
ARTG Number (s)	114714, 114717 and 114721

[1] The **full indications** are now:

Non-small cell lung cancer:

Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.

Tarceva is indicated for maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy. Efficacy is influenced by tumour characteristics (see CLINICAL TRIALS).

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

Pancreatic cancer:

Tarceva in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Product background

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

The currently approved indication for Tarceva is for use in non small-cell lung cancer as second-line treatment after the failure of first-line chemotherapy and as maintenance therapy in patients who have received first-line chemotherapy and have not progressed.

This AusPAR describes an application by the sponsor for an extension of these indications to include first-line use in the sub-population of NSCLC patients with activating mutations of the EGFR as follows:

> *Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.*

Erlotinib for the proposed indication was granted orphan designation on 14 April 2011.

No new dosage forms or strengths are proposed. The proposed dosage and administration for Erlotinib for the new indication is 150 mg orally per day on a continuous basis.

Iressa (gefitinib) is a similar product to Erlotinib but is restricted to NSCLC patients with activating EGFR mutations in both first and second-line use:

> *"Treatment of patients with locally advanced or metastatic NSCLC whose tumours express activating mutations of the EGFR tyrosine kinase".*

The TGA has adopted the European Medicines Agency (EMA) Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWG/205/95)[2] which is relevant to this application.

Regulatory status

The following table (Table 1) summarised the international regulatory status of this product.

Table 1. Summary of Overseas Status

Country	Status
European Union (EU) including the United Kingdom (UK)	Approved 24 August 2011
Switzerland	Approved 3 February 2012

Product Information

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

[2] <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf>

II. Quality findings

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

III. Nonclinical findings

Introduction

The nonclinical data submitted by the sponsor consisted of 19 literature references. Three references focussed on Erlotinib activity on EGFR mutants were evaluated, while the remaining papers were considered supportive. No major deficiencies were identified.

Pharmacology

Rationale

Somatic mutations in EGFR have been identified in up to 10% of NSCLC patients and >80% of these mutations are either an in-frame deletion mutation of exon 19 or a point mutation in exon 21 (cited in Carey et al., 2006)[3]. Two of the most commonly occurring EGFR somatic mutations, EGFR L858R and EGFR del in exon 19, enhance downstream EGFR signalling pathways, promoting cell growth and proliferation.

Primary pharmacology

Nineteen EGFR mutants that have been reported in tumours from NSCLC patients were examined for oncogenic potential. Only 14 were found to be oncogenic, while four had no kinase activity. This suggests that at least 5 EGFR mutations that have been identified in tumours from NSCLC patients are not activating mutations. Erlotinib inhibited ligand-independent cell proliferation of 12/14 EGFR variants with activating mutations, with 50% inhibitory concentration (IC50) values less than the maximum plasma concentration of free Erlotinib at a 150 mg/day dose[4]. Erlotinib had no inhibitory activity at EGFR T790M and poor activity at EGFR N826S. The profile of inhibitory activity of Erlotinib at these EGFR variants was similar to that seen with gefitinib. Erlotinib had greater inhibitory activity (6–137 times lower inhibitor constant (Ki) for Erlotinib/Michaelis constant (Km) for adenosine triphosphate (ATP) ratio) at the two most common EGFR mutants (L858R and del in exon 19) than wild-type EGFR.

Erlotinib was assessed for its inhibitory effect on tumour growth in mice bearing SC grafts of cells expressing wild-type human EGFR, EGFR L858R or EGFR del in exon 19, and in mice containing pneumocytes expressing EGFR L858R or EGFR del in exon 19. In mice bearing SC grafts, Erlotinib had greater inhibitory activity on tumour growth in EGFR L858R and EGFR del in exon 19 expressing tumours than wild-type EGFR expressing tumours. The minimum effective doses were 150, 25 and 12 mg/kg/day orally (PO) in mice bearing wild-type EGFR, EGFR L858R and EGFR del in exon 19 expressing tumours, respectively. Significant reduction in tumour size was seen in Erlotinib-treated mice with lung tumours expressing EGFR L858R or EGFR del in exon 19. Taken together, the data

[3] Carey, K.D., A.J. Garton, M.S. Romero, J. Kahler, S. Thomson, S. Ross, F. Park, J.D. Haley, N. Gibson and M.X. Sliwkowski. (2006) Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, Erlotinib. *Cancer Res.* **66:** 8163-8171.

[4] The maximum plasma concentration of free Erlotinib at a clinical dose of 150 mg/day was 145 ng/mL (370 nM) (Clinical Study OSI2298g).

support the use of Erlotinib for the treatment of patients with tumours expressing the activating mutants of EGFR – EGFR L858R and EGFR del in exon 19.

EGFR mutation testing

It is stated in the PI document that EGFR mutation testing should be performed prior to initiation of Erlotinib (Tarceva) therapy in chemonaive patients with advanced or metastatic NSCLC. It is unclear how testing will be achieved, whether there is a validated commercially available kit or whether testing will be for all activating mutations. Further clarification from the sponsor may be required. This is brought to the attention of the Delegate.

Nonclinical summary and conclusions

- The nonclinical submission consisted of literature references, 3 of which were evaluated. No major deficiencies were identified.
- Analysis of 19 EGFR mutants, indicated not all EGFR mutations identified in NSCLC patients are activating mutations. Of the fourteen activating mutations examined, Erlotinib had clinically relevant inhibitory activity at 12 of these. No activity was seen at EGFR T790M and poor activity was seen at EGFR N826S.
- Erlotinib had significant tumour growth inhibitory activity in mice bearing EGFR L858R or EGFR del in exon 19.
- Taken together, the data generally support the proposed indication. Erlotinib had inhibitory activity at most, but not all, EGFR activating mutations.
- There are no nonclinical objections to the proposed extension of indication for Erlotinib.

IV. Clinical findings

Introduction

Clinical rationale

Erlotinib is an orally active potent selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-PK). Early clinical trials of Erlotinib and other EGFR antagonists in unselected patients with advanced NSCLC demonstrated striking activity in a sub set of patients who were of Asian descent, predominantly female with no or very limited smoking history. Further research demonstrated the clinical benefit was related to activating mutations of the EGF receptor. The most significant of these mutations are deletions in Exon 19 and a point mutation in Exon 21. Further studies including some in the first-line setting for patients with advanced stage NSCLC have shown that EGFR TKIs confer greater progression free survival and response rate benefit compared to chemotherapy in patients harbouring EGFR activating mutation. In view of this preliminary evidence of significant benefit, it is proposed that a randomised first-line study be undertaken in which patients would be appropriately randomised to receive Erlotinib or platinum based chemotherapy in patients with advanced stage NSCLC.

Scope of clinical dossier

The clinical submission contained full clinical reports of the submitted pivotal study ML20650 known as the EURTAC study, which is a Phase III multicentre open label randomised study of Erlotinib treatment versus chemotherapy in patients with advanced NSCLC who present with mutations in the tyrosine kinase domain of the EGFR. Full clinical report together with tabular summaries and synopses were provided.

An updated report is provided of an earlier pivotal study, namely Study BO18192 also known as SATURN, which is a pivotal study supporting the maintenance indication previously evaluated. This study contains data on patients with activating mutations of EGFR and an update on the previous study presented involving a further five months worth of data is presented. Relevant clinical report together with synopses and tabular summaries are provided.

All aspects of good clinical practice were observed.

Pharmacokinetics

No new data submitted.

Pharmacodynamics

No new data submitted.

Efficacy

A single pivotal study is provided for this proposed indication being Study ML20650 sponsored by the Spanish Lung Cancer Group and known as the EURTAC study. This is a multicentre open label active controlled randomised trial designed to determine if EGFR mutations can be used to improve treatment selection for patients with advanced NSCLC.

Patients were initially screened by a central laboratory and had confirmed the Exon 19 deletion or Exon 21 point mutation in the EGFR TK domain, fulfilling all inclusion criteria and no exclusion criteria and who were then randomised to receive either Erlotinib or chemotherapy.

Randomisation was stratified according to ECOG performance status[5] as well as deletion in Exon 19 versus point mutation in Exon 21.

[5] 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

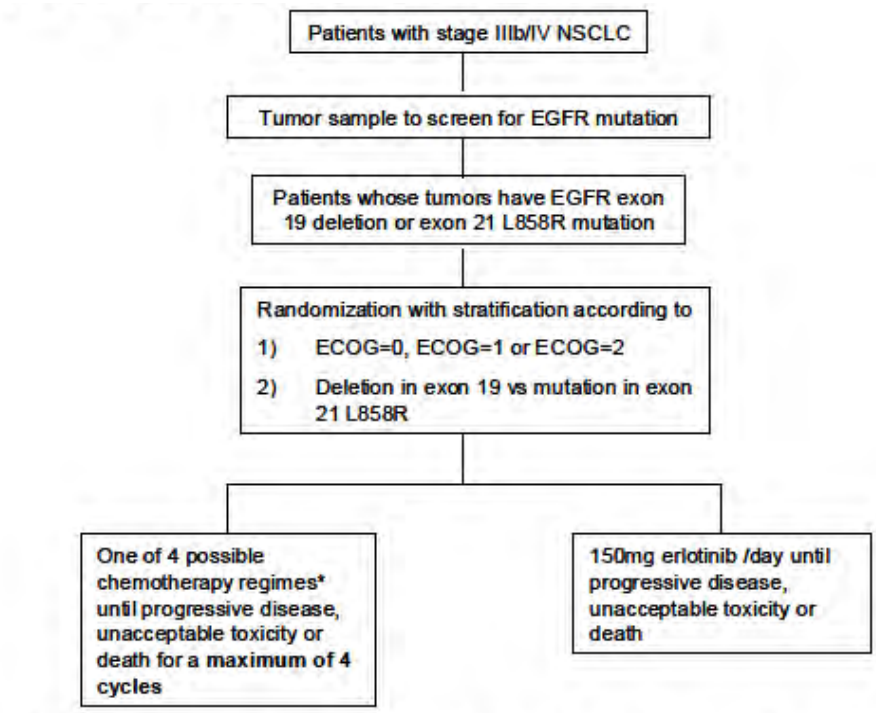
5 – Dead

Patients who received Erlotinib were given 150 mg per day orally until disease progression, unacceptable toxicity, patient withdrawal or death.

Patients in the chemotherapy arm received 1 of 4 possible regimens including Cis or Carboplatin plus Docetaxel together with Gemcitabine in standard dosage regimens. Chemotherapy was maintained until disease progression, unacceptable toxicity, patient withdrawal or death or a maximum of four treatment cycles whichever occurred first.

After initial screening, patients who were randomised to trial underwent clinical assessments every six weeks until confirmation of disease progression and thereafter patients were followed every three months until death. Full details of the design of study are given in Figure 1.

Figure 1. Design of Study ML20650 (EURTAC)



* Patients in the chemotherapy arm received one of the following chemotherapy regimens:

- Cisplatin plus docetaxel: cisplatin 75 mg/m^2 intravenous (i.v.) Day 1 and docetaxel 75 mg/m^2 i.v. Day 1. Repeat cycles every 3 weeks.
- Cisplatin plus gemcitabine: cisplatin 75 mg/m^2 i.v. on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8. Repeat cycles every 3 weeks.

The primary objective of the study was to compare investigator assessed progression free survival (PFS) in the two treatment arms of the study in patients who had not received previous chemotherapy or other systemic anti-tumour treatment for their disease and whose tumours had activating mutations in the TK domain of EGFR.

Secondary objectives included investigator assessed objective response; overall survival including one and two year survival rates; location of progression; safety profiles; gene mutation analysis of EGFR in serum and quality of life evaluations.

The target population for the study were patients with histologically documented NSCLC Stage IV or IIIB with malignant pleural effusions or M3 tumours, were not candidates for thoracic irradiation and if tumours presented with Exon 19 deletions or Exon 21 point mutations in the EGFR TK domain. They required measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, an ECOG performance status of no greater than 2; adequate renal, hepatic and bone marrow function.

Patients were randomised in a 1:1 ratio to receive either Erlotinib 150 mg per day orally until disease progression, unacceptable toxicity or death or chemotherapy according to the above indicated proposed protocols. Randomisation was stratified according to ECOG and mutation status as indicated above.

Tumour responses were evaluated according to RECIST criteria.

Patients were screened essentially to detect EGFR mutations with paraffin imbedded tumour samples being sent to a central laboratory.

The primary efficacy parameter of progression free survival (PFS) was defined as the time from randomisation to the first recurrence of progressive disease as assessed by both radiological and clinical progression or death from any cause whichever occurred first. Patients who had neither progressed nor died at the time of analysis were censored at the date of the last tumour assessment where non-progression was documented. PFS was analysed according to the Intent-to-Treat (ITT) population. Primary efficacy analysis was a non-stratified two-sided log-rank test for testing the hypothesis of equality of survival distribution of PFS based on the study investigator's assessment of tumour response. Cox regression analyses were undertaken for stratification factors including hazard ratios.

An independent review committee (IRC) assessed PFS.

Among the secondary efficacy parameters, overall survival was defined as a time between randomisation and the date of death, irrespective of the cause of death as determined by the study investigator. Objective response rate was determined by the study investigator according to the best overall response of either complete response (CR) or partial response (PR). Patients with a best overall response of either stable disease (SD) or progressive disease (PD) or their data was missing were assumed to be non-responders.

Location of progression was documented according to the organ involved as well as how many organs had progression.

Quality of life analyses were undertaken utilising a lung cancer symptom scale (LCSS) with symptomatic progression being defined as a worsening in the average symptom burden index by at least 25%.

The study was powered at 80% to demonstrate a median PFS in the Erlotinib arm of 10 months compared with six months in the chemotherapy arm corresponding to a Hazard Ratio (HR) of 0.6. This calculated a total of 135 PFS events were required, which corresponded to a sample size of 174 patients.

According to protocol one pre-specified interim analysis was planned after 88 PFS events were observed across both arms. If interim analysis was positive, recruitment into the study was to be stopped. Results were to be made public. Otherwise recruitment into the study would continue until 174 patients were recruited and the final analysis was to be formed when a total of 135 events had occurred across both arms.

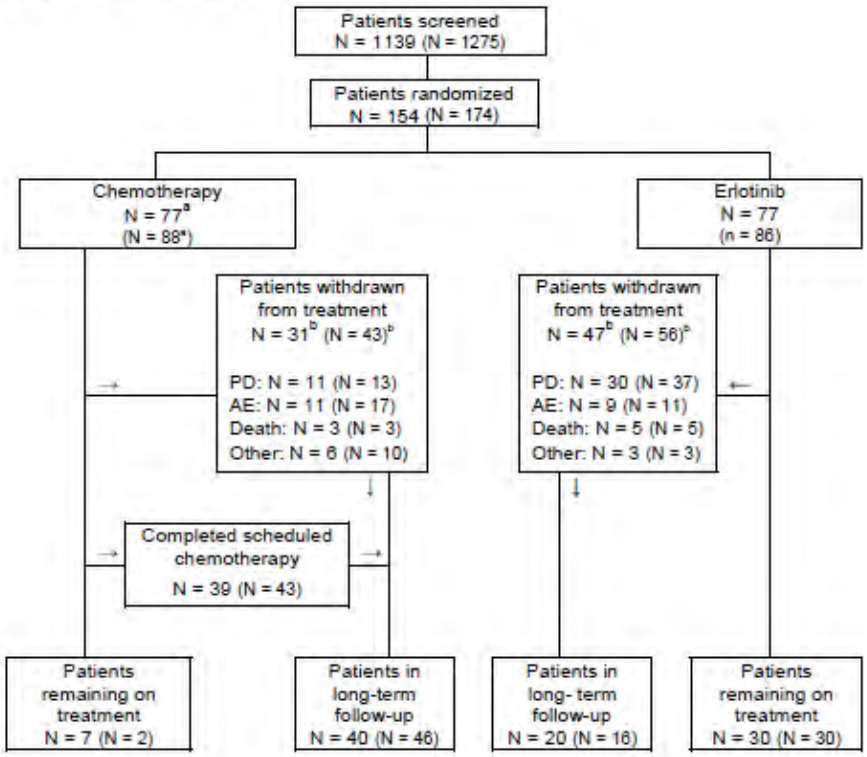
This interim analysis was performed by an independent statistician including all study data prior to the cut-off date of 2 August 2010. By this point, 92 PFS events had occurred. The results were provided to the independent data monitoring committee on the 24 January 2011 and following review of the interim results it was decided that recruitments should be ceased and full evaluation of study data and publication of full results undertaken.

An updated analysis of the study with a clinical cut-off date of 26 January 2011 has been subsequently performed in order to provide additional efficacy and safety information.

At the time of data cut-off of 2 August 2010 for the interim or primary analysis, a total of 1139 patients had been screened for study and 154 with EGFR activating mutations randomised with 77 patients to each arm. Patients' disposition is illustrated in Figure 2. Patients have been recruited from 42 centres in three countries; Spain, France and Italy.

The median duration of follow up was 10.7 months for the chemotherapy patients and 14.3 months for the Erlotinib patients. At the data cut-off of 2 August 2010, 28 patients in the chemotherapy arm and 27 in the Erlotinib arm had died in the all patient population, and 47 and 45 PFS events had been observed in the chemotherapy and Erlotinib arms respectively.

Figure 2. Patient disposition in Study ML20650



Note: Figures in parentheses represent data at the time of the cut-off for the exploratory updated analysis (January 26, 2011).

[a] One patient received chemotherapy prior to randomization.

[b] The imbalance in the number of treatment discontinuations due to PD or death is due to the fact that the chemotherapy treatment period was a maximum of 4 cycles (12-week treatment) and the erlotinib treatment period continued until disease progression.

'Other' reasons for the 6 patients withdrawn from the chemotherapy arm at the interim (primary) analysis were withdrawal of consent (2 patients), investigator criteria (2 patients [lack of efficacy and toxicity]) and other reasons (2 patients). An additional 4 patients had been withdrawn from the chemotherapy arm at the time of exploratory updated analysis: withdrawal of consent (3 patients) and other reasons (1 patient).

'Other' reasons for the 3 patients withdrawn from the erlotinib arm included withdrawal of consent (1 patient), discontinuation of treatment to undergo surgery and radiotherapy (1 patient) and 1 protocol violation (stage IIIb NSCLC without pleural effusion).

At the time of the cut-off for the interim (primary) analysis 2 patients in the chemotherapy arm and no patients in the erlotinib arm were lost to follow–up. At the cut-off for the exploratory updated analysis, an additional 1 patient in the chemotherapy arm and 1 patient in the erlotinib arm were lost to follow-up.

At the time of the updated analysis for the cut-off date of 26 January 2011, a total of 1275 patients had been screened and 174 randomised on to study. The median duration of follow-up for the updated analysis being 14.4 months for chemotherapy patients and 18.9 months for Erlotinib patients. Thirty-two chemotherapy patients and 38 Erlotinib patients had died in the all patient population, and 59 and 52 PFS events were observed in the chemotherapy and Erlotinib arms respectively.

In the updated analysis as in the interim analysis, only one patient randomised to receive chemotherapy was not included in the ITT population.

Demographics data indicated that more females than males were involved in the study. Median age for the study was 64 years for chemotherapy patients and 65 years for the Erlotinib patients. Treatment arms were well balanced with respect to the demographic characteristics with the exception of gender and smoking status.

There were no notable differences in the demographic characteristics between the populations of the interim analysis and the updated analysis. The updated analysis between arms remained well balanced with respect to demographic characteristics excepting gender and smoking status.

Review of the balance of stratification factors in the primary population again demonstrated good balance generally. As with the interim analysis a good balance of stratification factors was achieved across both treatment arms in the updated analysis.

With regards to pre treatment factors including histology and stage of disease, these are illustrated for the two treatment arms in Table 2. The median time from first diagnosis of NSCLC was five weeks and 5.29 weeks in the chemotherapy and Erlotinib arms respectively with adenocarcinoma being the most common tumour type. Baseline tumour characteristics were well balanced between the treatment arms with respect to the number of target lesions and sites of disease. There was a small imbalance between the chemotherapy and Erlotinib arms in relation to the number of affected organs and this is illustrated in Table 3.

Table 2. Summary of Histology and Stage of NSCLC (FAS)-Interim (primary) analysis.

	CHEMOTHERAPY N = 76	ERLOTINIB N = 77
Weeks since First Diagnosis of NSCLC		
Mean	22.45	21.83
SD	87.987	46.296
SEM	10.093	5.276
Median	5.00	5.29
Min-Max	0.9 - 727.9	1.6 - 211.3
n	76	77
History of NSCLC		
SQUAMOUS CELL CARCINOMA	-	1 (1%)
ADENOCARCINOMA	67 (88%)	73 (95%)
LARGE CELL CARCINOMA	1 (1%)	3 (4%)
OTHER	6 (8%)	-
BRONCHIOLOALVEOLAR CARCINOMA	2 (3%)	-
n	76	77
Stage of NSCLC at Baseline		
M3 NOT CANDIDATE FOR THORACIC RADIOTHERA	-	1 (1%)
STAGE IIIB (WITH PLEURAL EFFUSION)	5 (7%)	6 (8%)
STAGE IV (METASTATIC)	71 (93%)	69 (91%)
n	76	76[a]
Histopathological Grade of NSCLC at BL		
G1: WELL DIFFERENTIATED	4 (5%)	10 (13%)
G2: MODERATELY DIFFERENTIATED	17 (22%)	16 (21%)
G3: POORLY DIFFERENTIATED	15 (20%)	15 (19%)
G4: UNDIFFERENTIATED	1 (1%)	3 (4%)
GX: NON-EVALUABLE DIFFERENTIATION	-	3 (4%)
UNKNOWN	39 (51%)	30 (39%)
n	76	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Cut-off for statistical analysis: 02AUG2010
DM16 03FEB2011:20:51:16
[a] Note added by PDRD: Patient 111740/0033 did not have documented stage IIIb or stage IV NSCLC at baseline

Table 3. Summary of baseline tumour status (FAS). Interim (primary) Analysis.

	CHEMOTHERAPY N = 76	ERLOTINIB N = 77
Sum of Longest Diameter (mm)		
Mean	73.6	69.6
SD	41.03	43.08
SEM	4.90	5.19
Median	70.0	60.0
Min-Max	10 - 194	12 - 225
n	70	69
Number of Target Lesions		
0	6 (8%)	8 (10%)
1	22 (29%)	26 (34%)
2	21 (28%)	18 (23%)
3	11 (14%)	15 (19%)
4	9 (12%)	5 (6%)
5	5 (7%)	4 (5%)
6	2 (3%)	1 (1%)
n	76	77
Non-target Lesions		
YES	68 (89%)	63 (83%)
NO	8 (11%)	13 (17%)
n	76	76
Number of Affected Organs		
1	18 (24%)	24 (31%)
2	25 (33%)	32 (42%)
3	20 (26%)	13 (17%)
4	12 (16%)	4 (5%)
5	1 (1%)	3 (4%)
7	-	1 (1%)
n	76	77
Site: Lung or Pleura		
YES	72 (95%)	74 (96%)
NO	4 (5%)	3 (4%)
n	76	77
Site: Liver		
YES	18 (24%)	9 (12%)
NO	58 (76%)	68 (88%)
n	76	77
Site: Bone		
YES	25 (33%)	27 (35%)
NO	51 (67%)	50 (65%)
n	76	77
Site: Brain		
YES	8 (11%)	7 (9%)
NO	68 (89%)	70 (91%)
n	76	77
Site: Adrenal Gland		
YES	6 (8%)	4 (5%)
NO	70 (92%)	73 (95%)
n	76	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Visceral disease includes lesions of lung, pleura or liver.
Cut-off for statistical analysis: 02AUG2010
DM16 03FEB2011:20:55:50 (1 of 2)

	CHEMOTHERAPY N = 76	ERLOTINIB N = 77
Site: Lymph Nodes		
YES	39 (51%)	41 (53%)
NO	37 (49%)	36 (47%)
n	76	77
Site: Other		
YES	13 (17%)	3 (4%)
NO	63 (83%)	74 (96%)
n	76	77
Visceral Disease		
YES	73 (96%)	74 (96%)
NO	3 (4%)	3 (4%)
n	76	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Visceral disease includes lesions of lung, pleura or liver.
Cut-off for statistical analysis: 02AUG2010
DM16 03FEB2011:20:55:50 (2 of 2)

More patients in the Erlotinib arm received previous treatments including surgery and radiotherapy as compared to the chemotherapy arm being overall 33% versus 24%. Treatment arms were well balanced with regard to the proportion of patients who had one or more concomitant diseases, being 78% for chemotherapy patients and 74% for the Erlotinib patients.

Reviewing the efficacy results, the interim analysis of study data with a median follow-up of 10.7 months in the chemotherapy arm and 14.3 months in the Erlotinib arm demonstrated a significant advantage for those patients receiving Erlotinib versus chemotherapy with the risk of having a PFS event being significantly reduced by 58% with an HR 0.42 and 95% confidence interval (CI) 0.27-0.64 for patients in the Erlotinib arm compared to the chemotherapy arm with a p value <0.0001 by log rank test. This is illustrated in Table 4. The median PFS in the chemotherapy arm was 5.2 months compared to 9.4 months in the Erlotinib arm and 12% of patients in the chemotherapy arm and 37% in the Erlotinib arm were event free one year after randomisation. Kaplan-Meier curves of PFS began to separate around three months and remained well separated over the course of the observation period as indicated in Figure 3.

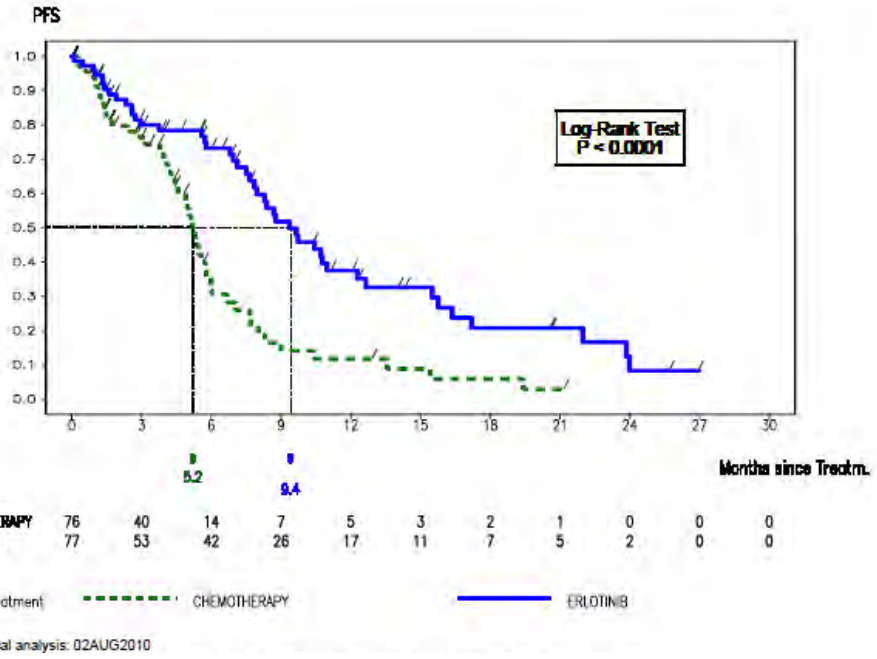
Table 4. Summary of PFS (FAS). Interim (primary) analysis.

	CHEMOTHERAPY (N=76)		ERLOTINIB (N=77)
Patients with event	47 (61.8 %)		45 (58.4 %)
Patients without event*	29 (38.2 %)		32 (41.6 %)
Time to event (months)			
Median#	5.2		9.4
95% CI for Median#	[4.4;5.8]		[7.9;12.3]
25% and 75%-ile	3.2;7.7		5.7;16.4
Range##	0.0 to 21.2		0.0 to 26.9
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.42	
95% CI		[0.27;0.64]	
1 year estimate			
Patients remaining at risk	5		17
Event Free Rate#	0.12		0.37
95% CI for Rate#	[0.02;0.21]		[0.24;0.51]

PFS [months] (TTPFS_M) - Censoring: PFS Censoring (1=PD/death) (CSPFS)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 02AUG2010

Figure 3 Kaplan-Meier Curve of Progression Free Survival (FAS) – Interim (primary) Analysis

eratepfs_g 2000 Kaplan-Meier Curve of PFS
Protocol(s): ML20650 (W20650C)
Analysis: Full Analysis Set



Cut-off for statistical analysis: 02AUG2010

Various sensitivity analyses were undertaken and all were consistent with those of the primary analysis.

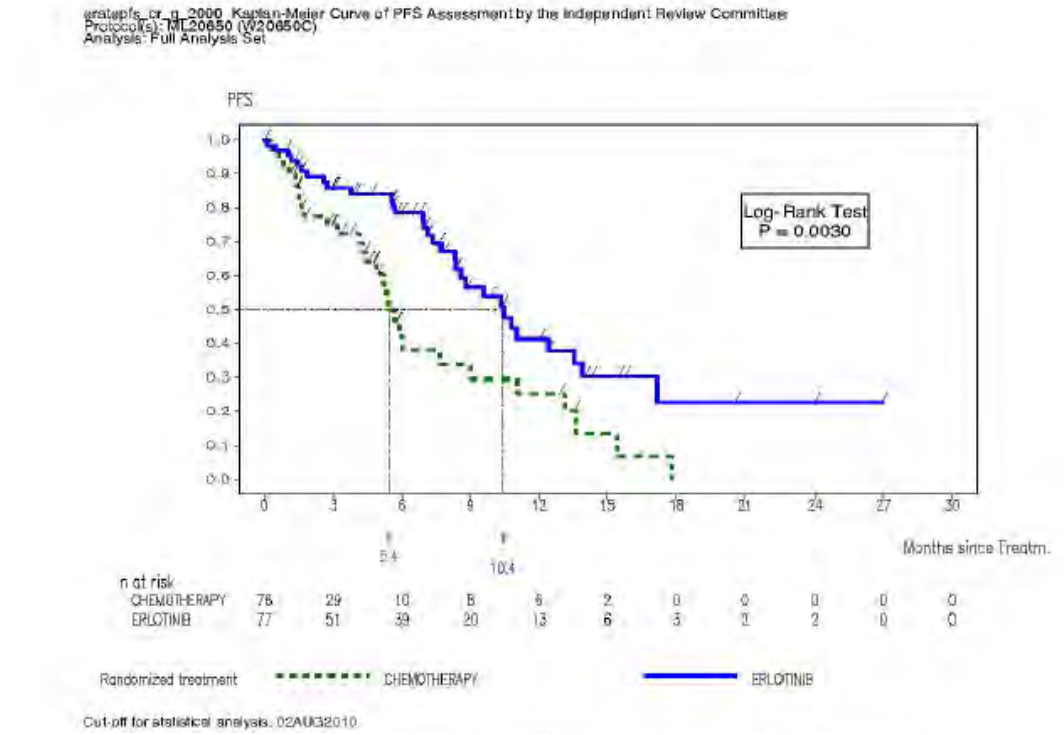
In order to assess the robustness of the primary PFS analysis a stratified PFS analysis was undertaken using stratification factors from randomisation. Results of this stratified analysis indicated a greater magnitude of benefit than that observed with the non-stratified analysis with an adjusted HR 0.39 and 95% CI 0.25-0.61 with p<0.0001 by log rank test.

A post hoc univariate Cox regression analysis of PFS was conducted as an additional robustness analysis adjusting for individual co-variates including stratification factors, demographic and baseline characteristics. The HR for the treatment effect was not meaningfully affected by any of the co-variates confirming the robustness of the primary analysis.

Not all patients for whom an investigator assessment was available had scans reviewed by the IRC. Overall at each time point a higher percentage of patients had tumour assessments reviewed by the IRC relative to the investigator in the Erlotinib arm compared to the chemotherapy arm.

Nevertheless these results of the IRC PFS analysis were consistent with the primary PFS analysis based on the investigator's assessment. At the interim analysis, 30 patients in the chemotherapy arm and 31 in the Erlotinib arm had a PFS event. The median PFS was 5.4 months in the chemotherapy arm compared to 10.4 months in the Erlotinib arm with a p value = 0.003 by log rank test with an HR 0.47 with 95% CI 0.28-0.78. 25% of patients in the chemotherapy arm and 41% of patients in the Erlotinib arm were event free after one year. The Kaplan-Meier curves began to separate approximately two months after treatment start as indicated in Figure 4.

Figure 4 Kaplan-Meier Curve of PFS Assessment by the IRC (FAS) – Interim (primary) Analysis

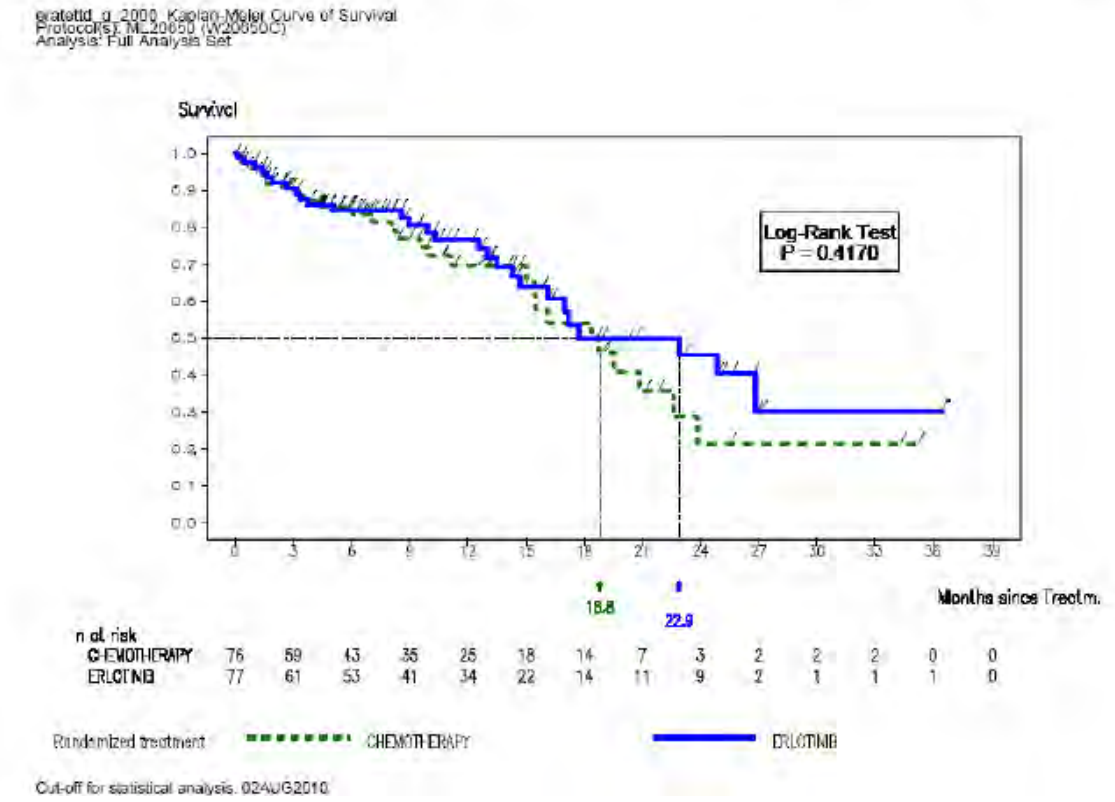


Results of the IRC PFS analysis stratified by ECOG status and mutation status were similar to those in the unstratified analysis with an HR 0.55 and a p value 0.027. In addition

results of the IRC PFS analysis based on the IRC's radiological review only were consistent with those of the primary IRC PFS analysis with an HR 0.55 and a p value 0.028.

Reviewing secondary efficacy parameters: Overall survival data was immature at the time of the interim analysis when 54 patients or 35% had died, 27 patients in each arm. The median time to death was 18.8 months for the chemotherapy arm compared to 22.9 months in the Erlotinib arm with an HR 0.80 and a p value 0.42. The one year event free rate was 0.70 in the chemotherapy arm compared to 0.77 in the Erlotinib arm. The Kaplan-Meier curves overlapped for approximately 19 months before they started to show some separation in favour of Erlotinib as indicated Figure 5. The two-year event free rate was 0.22 in the chemotherapy arm compared to 0.45 in the Erlotinib arm.

Figure 5 Kaplan-Meier Curve of Overall Survival (FAS) – Interim (primary) Analysis



In relation to best overall response, the proportion of patients achieving a best overall response of CR or PR was significantly greater in the Erlotinib arm than the chemotherapy arm; 54.5% versus 10.5% with a p value of <0.0001 and is indicated in Table 5. Results of best overall response as assessed by the IRC were consistent with those assessed by the investigator being 9.2% in the chemotherapy arm compared to 41.6% in the Erlotinib arm with the difference being 32.4% with a p value <0.0001.

Table 5. Summary of best overall response. Investigator assessment (FAS). Interim (Primary) Analysis.

	CHEMOTHERAPY (N=76)		ERLOTINIB (N=77)
Responders$	8 (10.5 %)		42 (54.5 %)
Non-Responders	68 (89.5 %)		35 (45.5 %)
95% CI for Response Rates*	[4.7; 19.7]		[42.8; 65.9]
Difference in Response Rates		44.02	
95% CI for Difference in Response Rates#		[30.2; 57.9]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		10.20	
95% CI for Odds Ratio		[4.32;24.06]	
Complete Response (CR)	0 (0.0 %)		2 (2.6 %)
95% CI for CR Rates*	[0.0; 4.7]		[0.3; 9.1]
Partial Response (PR)	8 (10.5 %)		40 (51.9 %)
95% CI for PR Rates*	[4.7; 19.7]		[40.3; 63.5]
Stable Disease (SD)	42 (55.3 %)		18 (23.4 %)
95% CI for SD Rates*	[43.4; 66.7]		[14.5; 34.4]
Progressive Disease (PD)	10 (13.2 %)		6 (7.8 %)
95% CI for PD Rates*	[6.5; 22.9]		[2.9; 16.2]
Missing (No Response Assessment)	16 (21.1 %)		11 (14.3 %)

Best Overall Response (BRESP)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of confirmed CR or PR
Non-Responder is SD, PD or missing.
Cut-off for statistical analysis: 02AUG2010

In relation to location of disease progression, a total of 47 patients on the chemotherapy arm and 35 on the Erlotinib arm experienced disease progression. The organ most commonly affected by disease progression was the lung and there was no obvious pattern of disease progression to other organs. In the chemotherapy arm there was more progression in the liver and less progression in the lymph nodes compared with the Erlotinib arm. The majority of disease progression was limited to one organ.

In relation to quality of life assessments the proportion of patients completing the quality of life questionnaire was low. The data therefore evaluated was essentially non-contributory.

Reviewing the results from the updated analysis as of the cut-off date of the 26 January 2011: The analysis of the investigator assessed PFS remained highly statistically significant in favour of Erlotinib with a p value of <0.0001 as indicated in Table 6. The risk of a PFS event was significantly reduced by 63% with an HR 0.37 and CI 0.25-0.54 for patients in the Erlotinib arm. Stratified and sub-group analysis supported the robustness of the results. The median PFS on the chemotherapy arm was 5.2 months compared to 9.7 months in the Erlotinib arm and the risk of having a PFS event was significantly reduced by 63% for patients in the Erlotinib arm. Some 11% of patients in the chemotherapy arm and 40% in the Erlotinib arm were event free in the one year after randomisation. The Kaplan-Meier curves for PFS began to separate at around three months and remained well separated over the course of the observation period as indicated in Figure 6. In relation to secondary efficacy parameters, the overall survival data remained immature at the exploratory updated analysis cut-off date with 69 patients or 39.9% of all patients having died, 31 in the chemotherapy arm and 38 in the Erlotinib arm. The median time to death was 19.5 months in the chemotherapy arm and 19.3 months in the Erlotinib arm with an HR of 1.04 and a p of value 0.8702 as indicated in Figure 7. The one year event free rate was 71% in the chemotherapy arm and 75% in the Erlotinib arm. The two year event free rate was 36% in the chemotherapy arm and 43% in the Erlotinib arm.

Table 6. Summary of efficacy results at updated analysis (data cut-off 26 January 2011).

Section	Parameter	Comparator Arm N = 87	Erlotinib Arm N = 86
Section 2.5.1	**Progression Free Survival in FAS (Investigator assessment)**		
	Patients with event	59 (67.8%)	52 (60.5%)
	Patients without event	28 (32.2%)	34 (39.5%)
	median (months)	5.2	9.7
	p-value (Log-Rank test)	< 0.0001	
	HR (95% CI):		
	Non-stratified	0.37 [95% CI 0.25 to 0.54]	
	Stratified	0.36 [95% CI 0.24 to 0.54]	
Section 2.5.2	**Overall Survival in FAS**		
	Patients with event	31 (35.6%)	38 (44.2%)
	Patients without event	56 (64.4%)	48 (55.8%)
	median (months)	19.5	19.3
	p-value (Log-Rank test)	0.8702	
	COX regression HR (95% CI):		
	Non-stratified	1.04 [95% CI 0.65 to 1.68]	
Section 2.5.3	**Best Overall Response (Investigator Assessment)**		
	Responders	13 (14.9%)	50 (58.1%)
	Non-responders	74 (85.1%)	36 (41.9%)
	Difference in response rate [approx 95% CI, Hauck-Anderson]	43.2 [29.7 to 56.7]	
	p-value (Chi-squared test)	< 0.0001	
	Complete response	0 (0%)	2 (2.3%)
	Partial response	13 (14.9%)	48 (55.8%)
	Stable disease	44 (50.6%)	18 (20.9%)
	Progressive disease	11 (12.6%)	6 (7.0%)
	Missing[a]	19 (21.8%)	12 (14.0%)

Note: p-values are based on non-stratified analysis

[a] Patients with a missing response assessment were counted as non-responders.

Figure 6 Kaplan-Meier Curve of Progression Free Survival (FAS) – Updated Analysis

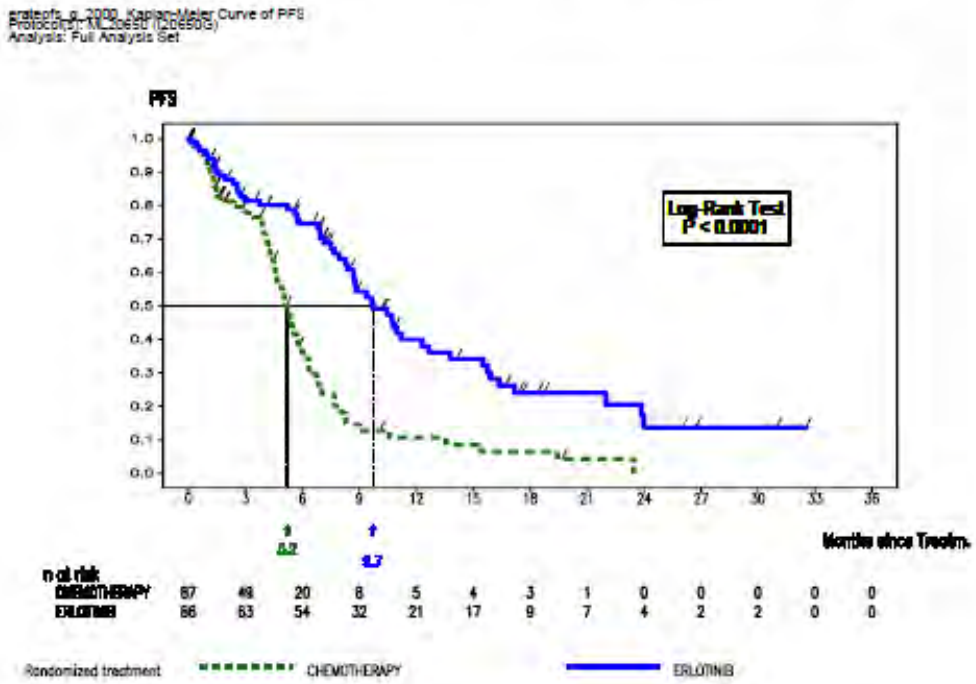
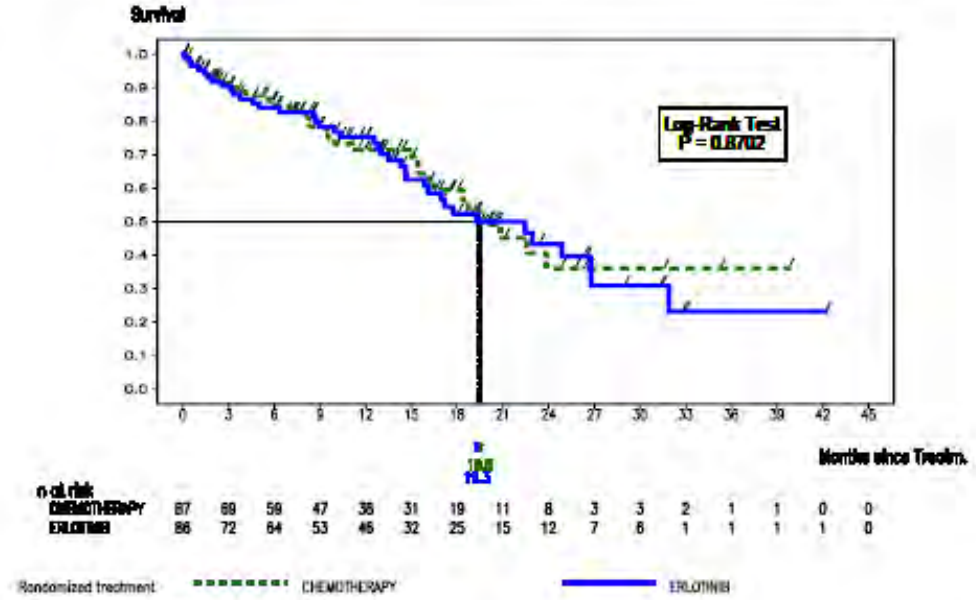


Figure 7 Kaplan-Meier Curve of Overall Survival (FAS) – Updated Analysis



In relation to best overall response rate, as for the interim analysis the response rate in the update analysis was significantly greater in the Erlotinib arm than the chemotherapy arm being 58.1% versus 14.9% with a p value of <0.0001 as indicated in Table 7. Overall the proportion of responders was slightly higher in both arms at the exploratory updated analysis compared to the interim analysis.

Table 7. Summary of best overall response (Investigator assessment) (FAS)-Updated analysis.

	CHEMOTHERAPY (N=87)		ERLOTINIB (N=86)
Responders$	13 (14.9 %)		50 (58.1 %)
Non-Responders	74 (85.1 %)		36 (41.9 %)
95% CI for Response Rates*	[8.2; 24.2]		[47.0; 68.7]
Difference in Response Rates		43.20	
95% CI for Difference in Response Rates#		[29.7; 56.7]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		7.90	
95% CI for Odds Ratio		[3.81;16.38]	
Complete Response (CR)	0 (0.0 %)		2 (2.3 %)
95% CI for CR Rates*	[0.0; 4.2]		[0.3; 8.1]
Partial Response (PR)	13 (14.9 %)		48 (55.8 %)
95% CI for PR Rates*	[8.2; 24.2]		[44.7; 66.5]
Stable Disease (SD)	44 (50.6 %)		18 (20.9 %)
95% CI for SD Rates*	[39.6; 61.5]		[12.9; 31.0]
Progressive Disease (PD)	11 (12.6 %)		6 (7.0 %)
95% CI for PD Rates*	[6.5; 21.5]		[2.6; 14.6]
Missing (No Response Assessment)	19 (21.8 %)		12 (14.0 %)

Best Overall Response (BRESP)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of confirmed CR or PR
Non-Responder is SD, PD or missing.
Cut-off for statistical analysis: 26JAN2011

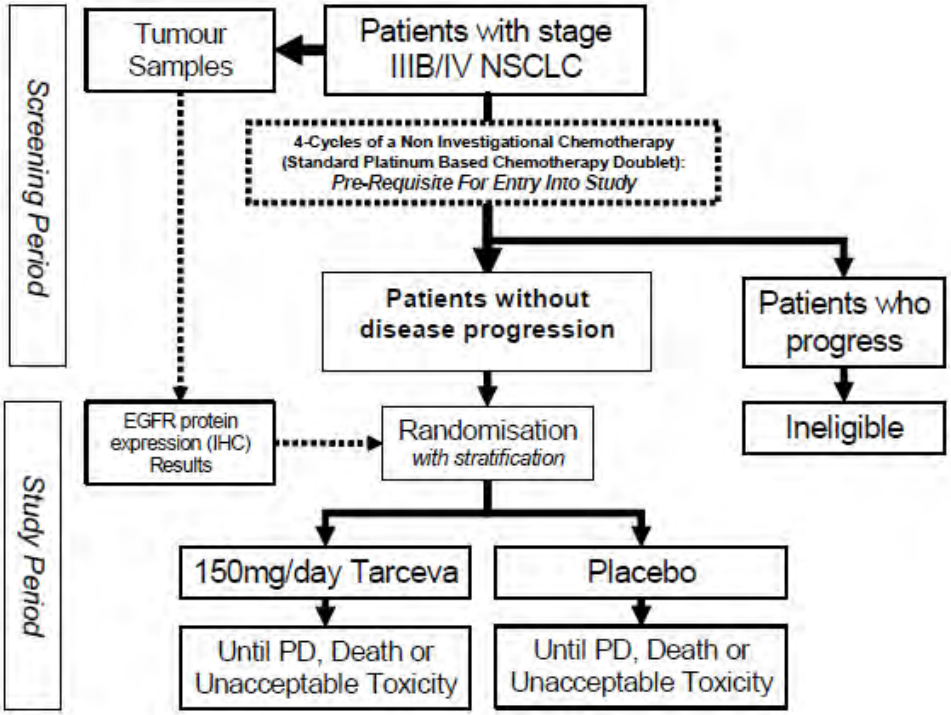
Further review of data was undertaken according to sub-group analysis of PFS by stratification factors, demographic and baseline characteristics, histology and previous treatment related to the NSCLC. These analyses confirmed the favourable effect of Erlotinib.

Evaluator comment:

The data from this pivotal study has clearly shown the influence of Erlotinib compared to chemotherapy in relation to the primary efficacy parameter of PFS that Erlotinib provided a significantly superior outcome. This is confirmed by various sub-group analyses in relation to the individual pre-treatment factors. Furthermore secondary efficacy parameters also support a significant benefit for Erlotinib compared to chemotherapy. Nevertheless at this time the overall survival data remains immature and therefore ongoing follow up results will be pertinent to ensure and confirm the superiority of Erlotinib.

Supportive data is provided from an earlier evaluated study namely BO18192 also known as SATURN, which is a multicentre randomised double blind placebo controlled Phase III study of single agent Erlotinib following four cycles of platinum based chemotherapy in patients with Stage IIIB or IV NSCLC. An overview of the study design is given in Figure 8. The co-primary efficacy endpoints were PFS according to RECIST in all patients and in the EGFR immunohistochemistry positive population according to investigator's assessment. An independent combined radiological and clinical assessment was undertaken to provide an independent assessment of response and disease progression. Secondary efficacy endpoints included overall survival in all patients and the EGFR IHC positive sub-population as well as PFS overall survival in the EGFR IHC negative sub-group, time to disease progression, time to symptom progression and response rates.

Figure 8. Study design

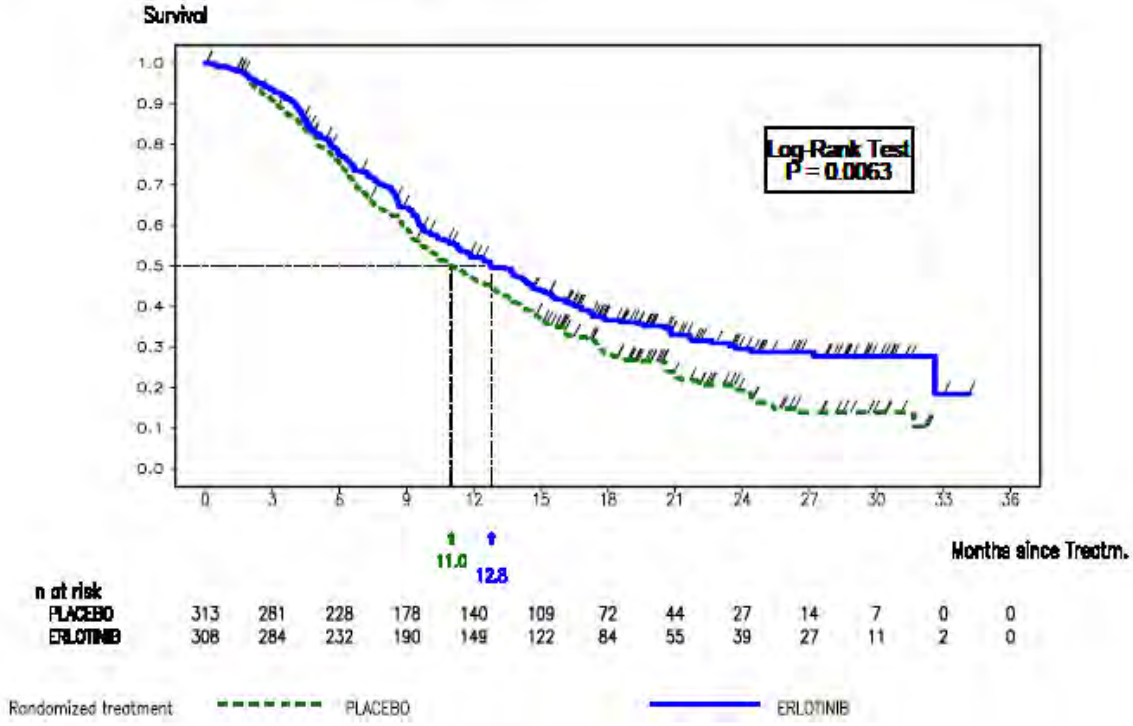


Results from this supportive study involve an updated analysis of final overall survival together with an update of progression free survival results by the EGFR mutation status as of the 17 May 2009.

Initially 889 patients had been randomised to receive either Erlotinib or placebo as maintenance therapy. At the final cut-off date for overall survival analysis of 17 May 2009, a total of 648 events of death had occurred of which 68% occurred on Erlotinib and 78% on placebo. In the overall population the HR for overall survival is 0.81 with a p value 0.0088 and median overall survival is 11 versus 12 months in the placebo and the Erlotinib arms.

In relation to overall survival and the EGFR IHC positive population, the HR for overall survival was 0.77 with a CI 0.64-0.93 and a p value 0.0063 as indicated in Figure 9. The median overall survival was 11 versus 12.8 months in the placebo and Erlotinib arms respectively.

Figure 9. Kaplan-Meier Curve of Overall survival in EGFR (IHC) Positive population.



In this study a pre specified sub-population analysis of the study was performed to evaluate treatment response in the patients with tumours with EGFR activating mutation. The patients with a known EGFR mutation status, 446 patients overall, 11% or 49 patients were identified with mutation positive tumours, 22 in the Erlotinib group and 27 in the placebo group. Analysis of progression free survival at the time of the original data cut-off was undertaken and demonstrated a median time to event of 13 weeks for the placebo group versus 44.6 weeks for the Erlotinib group with a HR of 0.1 and a p value <0.0001. A further progression free survival analysis for this sub-group was rerun on the updated clinical cut-off date of the 17 May 2009 and is summarised in Table 8. The PFS benefit from treatment with Erlotinib in the patients with EGFR mutated tumours remained highly significant with an HR 0.23 and p value <0.0001.

Table 8. Summary of PFS in the EGFR mutation positive subgroup, OS cut-off

Analysis: Full Analysis Set - EGFR mutated (activating)

	PLACEBO (N=27)		ERLOTINIB (N=22)
Patients with event	26 (96.3 %)		21 (95.5 %)
Patients without event*	1 (3.7 %)		1 (4.5 %)
Time to event (weeks)			
Median#	13.0		46.1
95% CI for Median#	[11.6;21.3]		[33.7;59.6]
25% and 75%-ile	6.1;22.8		32.6;59.9
Range##	5.3 to 64.9		13.0 to 95.3
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.23	
95% CI		[0.12;0.45]	
6 months estimate			
Patients remaining at risk	4		17
Event Free Rate#	0.17		0.77
95% CI for Rate#	[0.02;0.31]		[0.60;0.95]

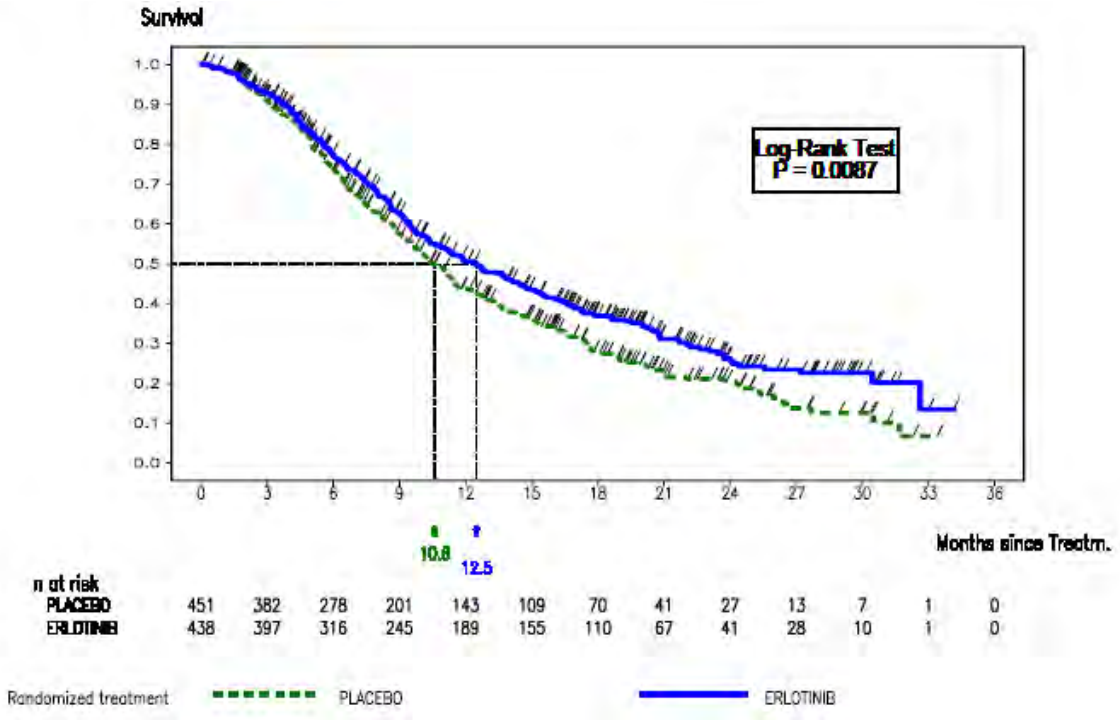
PFS [weeks] (TTPFS_W) - Censoring: PFS Censoring (prim. ana.,1=PD/death) (CSPFS)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2009

Review of overall survival data in the EGFR mutation positive sub-group whilst they were immature particularly in the Erlotinib arm, only 8/22 patients had died at time of cut-off and in addition 67% of placebo patients in the EGFR mutation positive sub-group received second or further line treatment with EGFR TKIs.

An updated overall survival analysis in patients with EGFR mutated tumours was performed in February 2011 and at this data cut-off, the rate of events was 70% in the placebo arm and 73% in the Erlotinib arm. The HR for overall survival in patients with EGFR activating mutations was 1.01 with 95% CI 0.52-1.97.

A further analysis of overall survival censored by open-label Erlotinib or second and further line tyrosine kinase inhibitors (TKI) inhibitors was conducted. This for the overall patient population revealed that there was a significant benefit for Erlotinib with an HR 0.80 and a p value 0.0087. The difference in median survival was 10.6 months in placebo and 12.5 months in Erlotinib and is illustrated in, Figure 10.

Figure 10. Kaplan-Meier Curve of Overall survival censored by first open label Erlotinib or second and further line tyrosine kinase inhibitors. FAS



Evaluator comment

This data including the update from the earlier Study BO18192 has confirmed evidence of a statistically significant progression free survival benefit for those patients with EGFR mutation positive status when receiving Erlotinib compared to placebo. There is also some evidence of survival benefit for the overall population of patients receiving Erlotinib in the maintenance setting but as this data is highly censored and to some extent statistically manipulated it is difficult to draw firm conclusions. Furthermore the number of patients in the EGFR mutation positive sub group is small and therefore does not provide sufficient evidence of a definite overall survival benefit with Erlotinib.

Safety

The safety data provided for this evaluation is that from the pivotal trial ML20650, the principal data from the interim analysis with a cut-off date of 2 August 2010. Updated data with regards to safety is also provided with a clinical cut-off date of 26 January 2011.

Adverse events were recorded by investigators and the severity of these adverse events graded according to NCI common toxicity criteria.

Dose reductions required for Erlotinib involved a decrease in dose by 50 mg per day and if there was no improvement in the particular toxicity then a further dose reduction by 50 mg per day was undertaken. A dose interruption for a maximum of two weeks was undertaken if clinically indicated. If a patient's dose interruption continued beyond two weeks without abatement of toxicity the treatment was withdrawn. Once a patient's dose had been reduced it remained at the reduced dose for the remainder of study.

The safety analysis population for the study composed all patients who had received at least one dose of study medication and at least one safety follow-up whether withdrawn prematurely or not. With 154 patients enrolled in study at the time of the primary analysis, 149 were included in the safety analysis, 75 receiving Erlotinib and 74 receiving chemotherapy. Five patients were excluded from the safety analysis population, three who

did not receive treatment on the chemotherapy arm and two on the Erlotinib arm, one who was not treated and one who had no follow-up. Of the 174 patients enrolled at the time of the updated analysis, two additional patients both randomised to chemotherapy arm were excluded because they did not receive treatment.

In relation to the extent of exposure at the time of the clinical cut-off date of the interim analysis, the median duration of treatment calculated from the first day of study treatment was 2.79 months for patients on chemotherapy and 7.62 months for patients receiving Erlotinib. As of 26 January 2011, the cut-off date for the updated analysis median duration of treatment was 2.54 months for patients on chemotherapy and 9.34 months for patients receiving Erlotinib. Of the 74 patients who received chemotherapy the distribution of the chemotherapy regimens is Table 9, with the majority of patients receiving Gemcitabine plus Cisplatin.

Table 9. Summary of planned chemotherapy combinations in Study ML20650-Interim (primary) analysis.

Protocol(s): ML20650 (W20650C)
Analysis: SAFETY ANALYSIS POPULATION Center: ALL CENTERS

	CHEMOTHERAPY N = 74
Planned chemotherapy treatment	
DOCETAXEL+CISPLATIN	15 (20%)
DOCETAXEL+ CARBOPLATIN	4 (5%)
GEMCITABINE+ CISPLATIN	31 (42%)
GEMCITABINE+ CARBOPLATIN	24 (32%)
n	74

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Cut-off for statistical analysis: 02AUG2010
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Note added by PDRD: one patient switched from cisplatin/gemcitabine to carboplatin/gemcitabine and is therefore counted twice in the summary of extent of exposure to chemotherapy.

A breakdown of dose reductions and dose modifications for the chemotherapies administered is given in Table 10.

Table 10. Summary of chemotherapy administration in Study ML20650-Interim (primary) analysis

	Dose Reduction[b]				Dose Delays[b]		
	None	≥ 0% and <25%	≥ 25% < 50%	≥ 50%	No	Delay < 2 weeks	Delay ≥ 2 weeks
Cisplatin	12 (80%)	2 (13%)	1 (7%)	1 (7%)	13 (87%)	2 (13%)	0
Docetaxel	12 (80%)	2 (13%)	1 (7%)	1 (7%)	13 (87%)	2 (13%)	0
N=15							
Carboplatin[a]	4 (100%)		0		2 (50%)	1 (25%)	1 (25%)
Docetaxel	4 (100%)	0	0	0	2 (50%)	1 (25%)	1 (25%)
N = 4							
Cisplatin	23 (74%)	5 (16%)	2 (6%)	2 (6%)	14 (45%)	17 (55%)	2 (6%)
Gemcitabine	22 (71%)	9 (29%)	0	2 (6%)	13 (42%)	18 (58%)	2 (6%)
N = 31							
Carboplatin[a]	20 (80%)		5 (20%)		14 (56%)	10 (40%)	1 (4%)
Gemcitabine	15 (60%)	6 (24%)	3 (12%)	8 (32%)	14 (56%)	11 (44%)	1 (4%)
N = 25							

[a] Percentage of dose reduction in mg/m^2 could not be calculated for carboplatin

[b] Number of patients with at least one dose reduction/delay. Zero doses, invalid doses and missed administrations are counted as dose reductions and not as dose delays.

Patients can contribute to more than one category

Patients who switched chemotherapy combination are counted for both regimens

In relation to Erlotinib exposure, the median cumulative dose of Erlotinib was 32,550 mg and 63% of patients received at least six months of treatment and 24% received at least 12 months of treatment. The median dose intensity of Erlotinib was 150 mg with a range 78-150 mg. Some 80% of the patients had no dose reduction while 20% had their dose reduced to 100 mg and 5% had their dose further reduced to 50 mg. Some 87% of patients had no dose interruption while 7% had dose interruption of less than one week, 11% dose interrupted for at least one week. In the updated analysis, 76% of patients had no reduction of Erlotinib dose while 24% had their Erlotinib dose reduced to 100 mg and 5% had it further reduced to 50 mg. Some 82% had no dose interruption while 13% had a dose interruption of less than one week and 11% had dose interruption for at least one week.

Reviewing the results of adverse events for the interim analysis, almost all patients in each treatment arm experienced at least one adverse event; 98.6% for chemotherapy and 96% for Erlotinib respectively. Adverse events encountered were generally consistent with the known safety profiles for chemotherapy and Erlotinib. Adverse events with an incidence rate of at least 10% are summarised in Table 11. Adverse events for which the incidence in the Erlotinib arm was clearly higher than the chemotherapy arm included various Skin and subcutaneous disorders including rash, dry skin, acne and pruritus as well as diarrhoea, cough, dyspnoea, mucosal inflammation, paronychia, back pain and conjunctivitis.

Table 11. Summary of adverse events with an incidence rate of at least 10% (all Grades and NCI-CTC Grade 3 or 4) in Study ML20650. Interim (primary) analysis

Protocol (s) : ML20650 (M20650C)
Analysis: SAFETY ANALYSIS POPULATION Center: ALL CENTERS

Body System/ Adverse Event	CHEMOTHERAPY N = 74 No. (%)			ERLOTINIB N = 75 No. (%)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
GASTROINTESTINAL DISORDERS						
DIARRHOEA	14 (18.9)	-	-	43 (57.3)	3 (4.0)	-
NAUSEA	30 (40.5)	4 (5.4)	-	17 (22.7)	1 (1.3)	-
VOMITING	16 (21.6)	3 (4.1)	-	10 (13.3)	-	-
CONSTIPATION	16 (21.6)	-	-	6 (8.0)	-	-
STOMATITIS	7 (9.5)	-	-	8 (10.7)	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
ASTHENIA	51 (68.9)	13 (17.6)	-	40 (53.3)	5 (6.7)	-
CHEST PAIN	10 (13.5)	-	-	13 (17.3)	1 (1.3)	-
PYREXIA	10 (13.5)	-	-	8 (10.7)	-	-
MUCOSAL INFLAMMATION	4 (5.4)	-	-	13 (17.3)	1 (1.3)	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
COUGH	26 (35.1)	-	-	34 (45.3)	1 (1.3)	-
DYSPNOEA	19 (25.7)	1 (1.4)	-	31 (41.3)	6 (8.0)	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
RASH	1 (1.4)	-	-	37 (49.3)	4 (5.3)	-
ALOPECIA	13 (17.6)	2 (2.7)	-	11 (14.7)	-	-
DRY SKIN	2 (2.7)	-	-	13 (17.3)	1 (1.3)	-
ACNE	-	-	-	9 (12.0)	-	-
PRURITUS	1 (1.4)	-	-	8 (10.7)	-	-
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
ANAEMIA	34 (45.9)	3 (4.1)	-	8 (10.7)	-	1 (1.3)
NEUTROPENIA	27 (36.5)	11 (14.9)	5 (6.8)	-	-	-
LEUKOPENIA	10 (13.5)	4 (5.4)	-	2 (2.7)	-	-
THROMBOCYTOPENIA	9 (12.2)	4 (5.4)	5 (6.8)	1 (1.3)	-	-
METABOLISM AND NUTRITION DISORDERS						
DECREASED APPETITE	25 (33.8)	-	-	21 (28.0)	-	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
BACK PAIN	4 (5.4)	-	-	12 (16.0)	-	-
INFECTIONS AND INFESTATIONS						
PARONYCHIA	-	-	-	12 (16.0)	-	-
EAR AND LABYRINTH DISORDERS						
TINNITUS	8 (10.8)	-	-	1 (1.3)	-	-
EYE DISORDERS						
CONJUNCTIVITIS	-	-	-	9 (12.0)	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010

Adverse events clearly of a greater incidence on the chemotherapy arm included haematological events such as anaemia, neutropenia, leukopenia and thrombocytopenia as well as asthenia, nausea, vomiting, constipation, decreased appetite and tinnitus. Throughout the study most adverse events were either Grade I or II in severity in relation to Erlotinib (91.2%) and chemotherapy (82%). Fewer patients in the Erlotinib arm experienced Grade III or greater adverse events; 41.3% compared to the chemotherapy arm being 66.2%. Some 16.2% of patients in the chemotherapy arm reported Grade IV adverse events compared to 6.7% in the Erlotinib arm. Seven patients in the Erlotinib arm had Grade V adverse events with death as the end result; one due to gastrointestinal haemorrhage, two pneumonia, one upper respiratory tract infection, one sepsis and one hepatotoxicity. There were four deaths in the chemotherapy arm from Grade V adverse events including one multi-organ failure, one respiratory failure, one cerebrovascular accident and one infection.

The body systems with the most common severe adverse events included Blood system with 31% of patients developing neutropenia and thrombocytopenia in the chemotherapy arm versus one patient in the Erlotinib arm. General disorders and administration site

conditions involved 15 patients in the chemotherapy arm versus eight patients in the Erlotinib arm and Gastrointestinal disorders involved 10 patients in the chemotherapy arm and five in the Erlotinib arm. Infections and infestations involved four patients in the chemotherapy arm versus 10 patients in the Erlotinib arm of which all were related to pneumonia.

A total 390 adverse events or 57.3% in the Erlotinib arm were assessed as remotely, possibly or probably related to treatment by the investigator compared with 351 adverse events or 66.6% in the chemotherapy arm. The majority of these related adverse events were assessed as Grade I or II in both arms of treatment.

Deaths which occurred during the treatment phase as assessed during the interim analysis included 7% of patients on the chemotherapy arm and 13% on the Erlotinib arm. The only death on the Erlotinib arm considered probably related to treatment was that of hepatotoxicity. Essentially all deaths which occurred in the follow-up phase were considered due to progressive disease. None were considered directly related to the previous treatment.

Reviewing serious adverse events in the interim analysis, 31 serious adverse events were reported among 19 patients with 25.7% on the chemotherapy arm and 28 serious adverse events reported among 20 patients or 26.7% in the Erlotinib arm as indicated in Table 12. As indicated, the most common of these in each treatment arm were Infections and infestations. Apart from the Blood and Lymphatic disorders occurring more frequently in the chemotherapy arm, overall there were no obvious imbalances in the frequency of serious adverse events across the two treatment arms. In the Erlotinib arm serious adverse events which were considered related to treatment included one event of Grade III diarrhoea, one event of Grade III respiratory tract infection, one event of Grade V hepatotoxicity, one event of Grade II hyperbilirubinemia and one Grade III lung disorder.

Reviewing adverse events leading to study withdrawal in the interim analysis, 11 patients (14.9%) of the chemotherapy arm and nine (12%) of the Erlotinib arm were withdrawn from study due to adverse event. On the Erlotinib arm, five patients were withdrawn for adverse events which were assessed by the investigator as unrelated to treatment and four events were probably related to treatment. One patient in the Erlotinib arm was withdrawn due to Grade III rash and one due to Grade III diarrhoea while mucosal inflammation and lung disorder were the remaining two adverse events probably related to treatment resulting in treatment withdrawal.

Adverse events leading to modification of study treatment revealed that in the chemotherapy arm more patients had dose modification and interruptions due to adverse events compared to the Erlotinib arm; 52% versus 27% respectively. Most chemotherapy patients with dose modifications (64.1%) had these due to haemalogical toxicities.

In the Erlotinib arm eight patients had dose modifications due to a rash and five due to diarrhoea, while other dose modifications in the Erlotinib arm involved single patients with a multiple number of reasons.

Table 12. Summary of serious adverse events in Study ML20650. Interim (primary) analysis. Table continued across two pages.

Body System/ Adverse Event	CHEMOTHERAPY N = 74 No. (%)	ERLOTINIB N = 75 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	19 (25.7)	20 (26.7)
Total Number of AEs	31	28
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	5 (6.8)	7 (9.3)
RESPIRATORY TRACT INFECTION	3 (4.1)	1 (1.3)
PNEUMONIA	-	2 (2.7)
DEVICE RELATED INFECTION	1 (1.4)	-
INFECTION	1 (1.4)	-
PYOTHORAX	-	1 (1.3)
SEPSIS	-	1 (1.3)
SUBCUTANEOUS ABSCESS	-	1 (1.3)
UPPER RESPIRATORY TRACT INFECTION	-	1 (1.3)
Total Number of AEs	5	7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	5 (6.8)	4 (5.3)
PULMONARY EMBOLISM	1 (1.4)	2 (2.7)
DYSPNOEA	-	2 (2.7)
RESPIRATORY FAILURE	2 (2.7)	-
HAEMOPTYSIS	1 (1.4)	-
LUNG DISORDER	-	1 (1.3)
PLEURAL EFFUSION	-	1 (1.3)
PNEUMONITIS	1 (1.4)	-
Total Number of AEs	5	6
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	5 (6.8)	1 (1.3)
FEBRILE NEUTROPENIA	3 (4.1)	-
THROMBOCYTOPENIA	3 (4.1)	-
ANAEMIA	1 (1.4)	1 (1.3)
Total Number of AEs	7	1
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	3 (4.1)	2 (2.7)
DIARRHOEA	-	1 (1.3)
GASTROINTESTINAL HAEMORRHAGE	-	1 (1.3)
GASTROINTESTINAL TOXICITY	1 (1.4)	-
GASTROOESOPHAGEAL REFLUX DISEASE	1 (1.4)	-
SIGMOIDITIS	1 (1.4)	-
Total Number of AEs	3	2
CARDIAC DISORDERS		
Total Pts With at Least one AE	1 (1.4)	3 (4.0)
CARDIAC TAMPONADE	-	2 (2.7)
CARDIAC FAILURE	1 (1.4)	-
PERICARDITIS	-	1 (1.3)
Total Number of AEs	1	3

Table 12. Summary of serious adverse events in Study ML20650. Interim (primary) analysis. Table continued.

Body System/ Adverse Event	CHEMOTHERAPY N = 74 No. (%)	ERLOTINIB N = 75 No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	2 (2.7)	2 (2.7)
CHEST PAIN	-	1 (1.3)
DEATH	-	1 (1.3)
MALAISE	1 (1.4)	-
MULTI-ORGAN FAILURE	1 (1.4)	-
Total Number of AEs	2	2
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	2 (2.7)	2 (2.7)
CEREBROVASCULAR ACCIDENT	2 (2.7)	1 (1.3)
POLYNEUROPATHY	-	1 (1.3)
Total Number of AEs	2	2
VASCULAR DISORDERS		
Total Pts With at Least one AE	2 (2.7)	1 (1.3)
DEEP VEIN THROMBOSIS	1 (1.4)	1 (1.3)
THROMBOSIS	1 (1.4)	-
Total Number of AEs	2	1
HEPATOBILIARY DISORDERS		
Total Pts With at Least one AE	-	2 (2.7)
HEPATOTOXICITY	-	1 (1.3)
HYPERBILIRUBINAEMIA	-	1 (1.3)
Total Number of AEs	-	2
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	1 (1.4)	1 (1.3)
RENAL FAILURE	-	1 (1.3)
RENAL FAILURE ACUTE	1 (1.4)	-
Total Number of AEs	1	1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		
Total Pts With at Least one AE	1 (1.4)	-
APLASIA	1 (1.4)	-
Total Number of AEs	1	-
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	1 (1.4)	-
DRUG HYPERSENSITIVITY	1 (1.4)	-
Total Number of AEs	1	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	-	1 (1.3)
FEMORAL NECK FRACTURE	-	1 (1.3)
Total Number of AEs	-	1
INVESTIGATIONS		
Total Pts With at Least one AE	1 (1.4)	-
PLATELET COUNT DECREASED	1 (1.4)	-
Total Number of AEs	1	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010
AE11 03FEB2011:20:56:44 (2 of 2)

In relation to adverse events of special interest three were identified as such including rash, interstitial lung disease and diarrhoea. In relation to rash 60 or 80% of patients in the Erlotinib arm experienced rash compared to two in the chemotherapy arm. The majority of these were Grade I or II although seven patients had Grade III rash. These were all generally considered related to treatment. Only one patient required treatment withdrawal due to rash. No events of interstitial lung disease were reported in the Erlotinib arm although there was one event of pneumonitis considered not related to treatment in the chemotherapy arm.

All patients in the Erlotinib arm experienced diarrhoea being 57.3% compared to the chemotherapy arm being 18.9%. The majority of these were Grade I or II although three events were Grade III. The majority of these events were assessed as probably related to

Erlotinib treatment. One patient in the Erlotinib group was withdrawn from trial treatment due to Grade III diarrhoea related to treatment.

Adverse events summarised by organ system are shown in Table 13. Body systems with the highest incidence of adverse events in the Erlotinib group were Skin and subcutaneous disorders being 82.7% and Gastrointestinal disorders being 69.3%, reflecting the fact that the most common adverse events among Erlotinib treated patients were rash 49.3% and diarrhoea 57.3%.

Table 13. Summary of Adverse event by body system. Interim (primary) analysis

Body System	CHEMOTHERAPY N = 74 No. (%)	ERLOTINIB N = 75 No. (%)
ALL BODY SYSTEMS	73 (98.6)	72 (96.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	59 (79.7)	53 (70.7)
GASTROINTESTINAL DISORDERS	50 (67.6)	52 (69.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	38 (51.4)	44 (58.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	17 (23.0)	62 (82.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	48 (64.9)	11 (14.7)
METABOLISM AND NUTRITION DISORDERS	30 (40.5)	25 (33.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	18 (24.3)	34 (45.3)
INFECTIONS AND INFESTATIONS	12 (16.2)	37 (49.3)
NERVOUS SYSTEM DISORDERS	21 (28.4)	20 (26.7)
INVESTIGATIONS	16 (21.6)	12 (16.0)
EYE DISORDERS	-	20 (26.7)
PSYCHIATRIC DISORDERS	12 (16.2)	8 (10.7)
EAR AND LABYRINTH DISORDERS	9 (12.2)	2 (2.7)
RENAL AND URINARY DISORDERS	6 (8.1)	2 (2.7)
VASCULAR DISORDERS	5 (6.8)	3 (4.0)
HEPATOBILIARY DISORDERS	-	7 (9.3)
CARDIAC DISORDERS	1 (1.4)	5 (6.7)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (1.4)	5 (6.7)
IMMUNE SYSTEM DISORDERS	2 (2.7)	1 (1.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.4)	2 (2.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (4.1)	-
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	-	2 (2.7)
ENDOCRINE DISORDERS	-	1 (1.3)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010

In relation to General disorders, more patients in the Erlotinib arm experienced mucosal inflammation; 17.3% compared to 5.4% for chemotherapy.

Among the incidence of diarrhoea affecting 57.3% of patients receiving Erlotinib, three of these were Grade III resulting in dose modification and one patient requiring treatment withdrawal.

The incidence of Infections and infestations was higher in the Erlotinib arm, 49.3% compared to 16.2% for chemotherapy, mainly due to the occurrence of paronychia and folliculitis.

In relation to Laboratory investigations more patients in the Erlotinib arm had elevation in liver function abnormalities including elevations of alanine aminotransferase (ALT) (5.3% versus 1.4% for chemotherapy) and gamma-glutamyl transferase (GGT) (4% versus 1.4% for chemotherapy).

Eye disorders were reported exclusively in the Erlotinib arm and particularly conjunctivitis affected 12% of patients.

In relation to hepatobiliary disorders, seven patients in the Erlotinib group had hepatic adverse events of which five were hyperbilirubinemia and one was considered serious being Grade II probably related to treatment. In addition, one patient had Grade V hepatotoxicity considered to be related to study treatment.

Reviewing adverse events from the updated safety analysis: Overall the safety profile of Erlotinib in this updated analysis was consistent with that from the interim analysis and its established safety profile. In relation to common adverse events these are summarised in Table 14 and as with the primary analysis. Gastrointestinal disorders were reported to a similar extent across both treatment arms with diarrhoea being more common in the Erlotinib arm as were Skin and subcutaneous disorders, particularly rash.

Table 14. Summary of adverse events with an incidence rate of at least 10%. Updated analysis.

Body System/ Adverse Event	CHEMOTHERAPY N = 83 No. (%)	ERLOTINIB N = 84 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	82 (98.8)	82 (97.6)
Total Number of AEs	629	811
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	67 (80.7)	60 (71.4)
ASTHENIA	59 (71.1)	47 (56.0)
CHEST PAIN	10 (12.0)	15 (17.9)
PYREXIA	14 (16.9)	9 (10.7)
MUCOSAL INFLAMMATION	5 (6.0)	14 (16.7)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	59 (71.1)	61 (72.6)
DIARRHOEA	17 (20.5)	48 (57.1)
NAUSEA	35 (42.2)	20 (23.8)
VOMITING	20 (24.1)	11 (13.1)
CONSTIPATION	17 (20.5)	7 (8.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	44 (53.0)	51 (60.7)
COUGH	29 (34.9)	39 (46.4)
DYSPNOEA	24 (28.9)	37 (44.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	21 (25.3)	72 (85.7)
RASH	2 (2.4)	46 (54.8)
ALOPECIA	15 (18.1)	12 (14.3)
DRY SKIN	2 (2.4)	15 (17.9)
PRURITUS	1 (1.2)	13 (15.5)
ACNE	-	9 (10.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	57 (68.7)	14 (16.7)
ANAEMIA	38 (45.8)	10 (11.9)
NEUTROPENIA	31 (37.3)	-
LEUKOPENIA	13 (15.7)	2 (2.4)
THROMBOCYTOPENIA	10 (12.0)	1 (1.2)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	33 (39.8)	32 (38.1)
DECREASED APPETITE	28 (33.7)	26 (31.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	22 (26.5)	39 (46.4)
BACK PAIN	4 (4.8)	14 (16.7)
ARTHRALGIA	5 (6.0)	9 (10.7)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	16 (19.3)	40 (47.6)
PARONYCHIA	-	12 (14.3)
EYE DISORDERS		
Total Pts With at Least one AE	-	23 (27.4)
CONJUNCTIVITIS	-	12 (14.3)
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	10 (12.0)	3 (3.6)
TINNITUS	9 (10.8)	1 (1.2)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 26JAN2011
AE11 09MAY2011:10:40:23 (PDRD 1 of 1)

In relation to deaths during the treatment phase as assessed by the updated analysis, one further death had occurred in Erlotinib arm the cause of which was unknown. During the survival follow-up phase no further patients on prior Erlotinib treatment died as a result of earlier pneumonitis considered probably related to Erlotinib although one death considered to be a pneumonopathy was probably secondary to the earlier pneumonitis.

At the time of the exploratory updated analysis, 26 patients or 31.3% had experienced 31 serious adverse events in the chemotherapy arm and 26 patients or 31% had experienced

28 serious adverse events in the Erlotinib arm and there were no notable differences in the types of serious adverse events between the interim analysis and the exploratory updated analysis.

In relation to adverse events of special interest, in the updated analysis, 83.3% of patients in the Erlotinib arm had experienced rash which can be compared to 80% of patients in the primary analysis. In relation to interstitial lung disease one patient was reported with pneumonitis having received Erlotinib not reported in the interim analysis.

In relation to clinical laboratory abnormalities in particular blood chemistry changes, those that occurred were generally Grade I or II in severity for both arms of treatment with few Grade III or IV laboratory parameter measurements. In the Erlotinib arm there were five Grade III measurements all related to hepatic function changes and two Grade IV measurements also related to disturbance in liver enzymes. As indicated earlier, one of these patients died due to hepatotoxicity.

In relation to haematological disorders these were predominantly related to the chemotherapy arm of study with 10 patients experiencing Grade III or IV changes leading to withdrawal of patients in three, two due to neutropenia and one due to thrombocytopenia, while two patients experienced haematological toxicity resulting in death; one due to cerebrovascular accident and one respiratory failure.

Review of changes in vital signs revealed no specific alterations of clinical consequence in either arm of study.

Reviewing adverse events in relation to gender, there was a slightly higher incidence of adverse events in the Erlotinib treated arm in females (98%) compared to males (91.7%) but there was no difference in the overall incidence of adverse events between gender in the chemotherapy arm. Those adverse events more frequently seen in females on Erlotinib included asthenia, cough, dyspnoea, conjunctivitis, dry skin, chest pain, decreased appetite and mucosal inflammation.

In relation to age, there was a higher incidence of adverse events among patients who were at least 65 years compared to those who were younger, more often seen among patients receiving Erlotinib; 100% for those >65 years versus 91.7% for those <65 years and for chemotherapy 100% versus 97.5%. Symptoms among the older patients receiving Erlotinib more commonly seen than for chemotherapy included asthenia, chest pain, mucosal inflammation, diarrhoea, dyspnoea, cough and decreased appetite.

In relation to extrinsic factors of possible significance it was noted that among patients who had never smoked receiving Erlotinib there was a slightly higher incidence of adverse events compared with past smokers who received Erlotinib (being 100% versus 89.5%)

Post marketing data

Erlotinib was first approved on 18 November 2004 and as of 1 April 2011 had been approved for marketing in more than 110 countries. Overall an estimated 625,000 patients had been treated with Erlotinib in the post marketing setting on clinical trials. Periodic safety updates are available through to 17 November 2010. Information regarding a patient's EGFR mutation status was not routinely collected during post marketing surveillance. However it is estimated that on the basis of the distribution of the post marketing population, approximately 30% and 10% of all Asian and Caucasian patients respectively with NSCLC may harbour tumours with activating EGFR mutations at initial diagnosis.

During the reporting period, that is, 18 November 2004 to 1 April 2011, a total of 28,129 adverse events of which 15,232 were serious were received. In total 2,673 deaths were reported of which the large proportion were due to progression of disease. The most frequently reported adverse events were those related to Skin and subcutaneous tissue

disorders particularly rash; Gastrointestinal disorders, particularly diarrhoea and General disorders including pyrexia and fatigue. Among Respiratory disorders, interstitial lung disease, dyspnoea and pulmonary embolism were infrequent events affecting 2.2%. These adverse events are illustrated Table 15.

Table 15. Summary tabulation of adverse events by System Organ Class.

System Organ Class	No. Patients with at least 1 AE/SOC	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
Infections and Infestations	1540	1151	7.6	1780	6.3
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	803	723	4.7	820	2.9
Blood and Lymphatic System Disorders	537	489	3.2	622	2.2
Immune System Disorders	33	20	0.1	33	0.1
Endocrine Disorders	19	13	0.1	19	0.1
Metabolism and Nutrition Disorders	1165	929	6.1	1373	4.9
Psychiatric Disorders	282	169	1.1	325	1.2
Nervous System Disorders	896	606	4.0	1035	3.7
Eye Disorders	677	177	1.2	868	3.1
Ear and Labyrinth Disorders	47	24	0.2	50	0.2
Cardiac Disorders	343	343	2.3	390	1.4
Vascular Disorders	392	342	2.2	417	1.5
Respiratory, Thoracic and Mediastinal Disorders	2183	2147	14.1	2654	9.4
Gastrointestinal Disorders	3697	2678	17.6	5344	19.0
Hepatobiliary Disorders	507	352	2.3	558	2.0
Skin and Subcutaneous Tissue Disorders	4323	1316	8.6	5661	20.1
Musculoskeletal and Connective Tissue Disorders	319	146	1.0	361	1.3
Renal and Urinary Disorders	284	233	1.5	299	1.1
Pregnancy, Puerperium and Perinatal Conditions	0	0	0	0	0
Reproductive System and Breast Disorders	57	18	0.1	62	0.2
Congenital, Familial and Genetic Disorders	28	10	0.1	28	0.1
General Disorders and Administration Site Conditions	3275	2591	17.0	3794	13.5
Investigations	934	600	3.9	1364	4.8
Injury, Poisoning and Procedural Complications	212	138	0.9	235	0.8
Surgical and Medical Procedures	34	15	0.1	34	0.1
Social Circumstances	3	2	0.0	3	0.0
Total	N/A	15232	100.0	28129	100.0

Evaluator comment

The safety data from this pivotal study including the interim and updated analyses essentially reflected the recognised safety profile for Erlotinib which has been well described previously from earlier clinical trials. Similarly the post marketing updates have confirmed this profile. Overall the majority of adverse events particularly the more common ones, namely rash and diarrhoea were generally Grade I and II with only occasional more severe events. The proportion of patients requiring treatment withdrawal was relatively low and it is noted that there were a small number of deaths of which hepatotoxicity is the most significant followed by the occasional case of interstitial lung diseases. These obviously require careful monitoring and early intervention as appropriate.

The data would suggest that the safety profile for Erlotinib is at least comparable to that for those patients receiving chemotherapy and in some areas probably of less severity.

Overall the safety data provided from this pivotal trial does not provide evidence of concern regarding the utilisation of Erlotinib in the proposed new indication.

List of questions

After an initial evaluation, a List of Questions to the sponsor is generated.

1. The only outstanding question relates to an update of overall survival analyses for Study ML20650.

Clinical summary and conclusions

First round benefit/risk assessment

First round assessment of benefits

Earlier data has demonstrated that the presence of activating mutations in the EGFR gene makes the receptor particularly susceptible to inhibition by EGFR tyrosine kinase inhibitors. Data suggested that the greatest benefit with agents such as Erlotinib is determined by the presence of this activating mutation. Accordingly the pivotal Phase III study presented in this submission, Study ML20650 randomly compared Erlotinib to standard chemotherapy in patients with advanced stage NSCLC who had not received prior chemotherapy for metastatic disease. The study was well planned and designed. A pre planned interim analysis undertaken by the independent data monitoring committee demonstrated clear evidence of benefit favouring Erlotinib resulting in earlier closure of the study. The data presented in this submission includes the full evaluation of the interim analysis data together with an updated assessment in relation to both efficacy and safety. The data demonstrated a statistically significant improvement in progression free survival and objective tumour response for patients receiving Erlotinib compared to chemotherapy with the risk of disease progression or death being reduced by 58% for those patients treated with Erlotinib and the median progression free survival based on investigator assessment being 9.4 months for patients receiving Erlotinib compared to 5.2 months for those receiving chemotherapy. The one year estimated event free rate was 12% in the chemotherapy arm compared to 37% in the Erlotinib arm. The investigator assessed primary endpoint progression free survival was corroborated by the independent review committee analysis and various sensitivity analyses also confirmed the superiority for Erlotinib.

Response rate data also demonstrated a significant benefit for Erlotinib with a response rate of 54.5% for Erlotinib vs 10.5% for chemotherapy with a p value <0.0001. Again this was supported by the independent review committee assessment.

The updated analysis with a data cut-off point of 26 January 2011 further supported the result of the primary efficacy analysis with the risk of disease progression being reduced by 63% for patients treated with Erlotinib versus the chemotherapy arm. Again response rates were significantly higher in patients receiving Erlotinib being 58.1% for Erlotinib versus 14.9% for chemotherapy.

In relation to overall survival the data was relatively immature and was similar in both treatment arms. At the interim analysis 54 patients or 35% had died and the HR was 0.80 which was not significant with a p value 0.42. In the updated analysis, 69 patients or 40% had died and again the HR was 1.04 with a p value 0.8702.

The supportive Study BO18192 involving a small sub-population of patients whose EGFR mutation status demonstrated evidence of activating mutations revealed that the progression free survival for those patients who received Erlotinib versus placebo in the

maintenance phase had a significantly longer progression free survival. The number of patients involved in this evaluation was relatively small but nevertheless was supportive of the data from the pivotal trial.

While further updated analyses evaluating overall survival results from the pivotal trial will be valuable, the clear cut evidence of benefit in relation to progression free survival achieved with Erlotinib in the first-line setting for patients with metastatic NSCLC with activating mutations of EGFR is sufficiently robust to warrant support for the proposed new indication.

First round assessment of risks

The evaluation of clinical safety data from the pivotal trial has identified that the toxicity profile observed for Erlotinib is generally consistent with that previously well recognised. Overall the safety profile appears to be associated with a somewhat lower overall incidence of adverse events particularly serious adverse events than that to be anticipated with standard chemotherapy. The highest incidence of adverse events for Erlotinib, namely rash and diarrhoea, were generally without major sequelae, although occasional serious adverse events of this nature warranted appropriate aggressive intervention. Careful monitoring for potential hepatotoxicity and pulmonary toxicity will be important in the clinical management of patients receiving Erlotinib.

This clinical evaluator considered that the safety profile demonstrated from the pivotal trial is such that there is no impediment to approval for Erlotinib in the first-line setting for patients with advanced stage NSCLC with activating mutations of EGFR.

First round assessment of benefit/risk balance

The benefits derived in this sub-population of patients with activating mutations of EGFR and advanced stage NSCLC has clearly benefited from the use of first-line Erlotinib resulting in significant improvements in progression free survival and response rates compared to standard chemotherapy. While data in relation to overall survival at this time was immature further updates will be awaited with interest. The safety profile does not provide an impediment to acceptance of the appropriate benefits from Erlotinib in this patient sub-population.

First round recommendation regarding authorisation

This clinical evaluator considered that the benefits derived in the population of patients with NSCLC who have activating mutations in the EGFR is such that the use of Erlotinib as a first-line treatment for the disease is of sufficient benefit to warrant approval for the proposed new indication.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows in the table below.

Table 16. Ongoing Safety Concerns

Important Identified Risks	Cutaneous toxicity
	Interstitial lung disease
	Liver injury
	GI Fluid loss
	GI perforations
	Ocular toxicity
	Interaction with coumarin derivative anticoagulants
	Interaction with statins
	Interaction with ketoconazole
	Interaction with ciprofloxacin
Important Potential Risks	Thrombotic microangiopathy
Important Missing Information	Pregnancy/Lactating
	Paediatrics
	Cardiac disorders

OPR reviewer comment

Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* to monitor all the specified ongoing safety concerns.

Guided questionnaires for medical professionals are proposed for use in follow-up of any report pertaining to the Important identified risks: 'Interstitial lung disease' and 'Liver injury' and the Important potential risk: 'Thrombotic microangiopathy'. The Australian Risk Managment Plan (RMP) Addendum confirms the use of these guided questionnaires in Australia. Copies of these guided questionnaires were provided in Annex 10 of the EU-RMP.

OPR reviewer's summary in regard to the pharmacovigilance plan (PP) and appropriateness of milestones

Given the proposed extension of indications and the target population, there is no objection to the sponsor implementing only routine pharmacovigilance activities to monitor all the specified Ongoing Safety Concerns.

Risk minimisation activities

The sponsor has provided justification and concluded that routine risk minimisation activities for all the specified Ongoing Safety Concerns are sufficient, except for the important identified risks: 'Cutaneous toxicity', 'Interstitial lung disease' and 'GI fluid loss', for which additional risk minimisation activities have also been proposed.

OPR reviewer comment

The Ongoing Safety Concerns for which additional risk minimisation activities have not been proposed would not appear to warrant additional risk minimisation activities. Therefore these conclusions were considered acceptable.

However, Table 67: 'A Summary of Planned Risk Minimisation Actions' should be amended to indicate that routine risk minimisation activities are not sufficient for the Important identified risks: 'Cutaneous toxicity', 'Interstitial lung disease' and 'GI fluid loss' to be consistent with Section 6: 'Risk Minimisation Plan' of the EU-RMP, which states:

Additional risk minimisation activities in the form of specialised educational materials for healthcare professionals and/or patients for identified ADRs (rash, diarrhoea and ILD) have been prepared to anticipate and manage these specific ADRs.

Sponsor's planned actions

Routine risk minimisation activities will include special warning and precaution statements, instructions for use and notification of drug interactions and/or undesirable effects in the Australian PI for all the specified Ongoing Safety Concerns.

For the Important identified risks: 'Cutaneous toxicity', 'Interstitial lung disease' and 'GI fluid loss' additional specialised educational materials for healthcare professionals and/or patients have been prepared to anticipate and manage these specific Adverse Drug Reactions (ADRs). It would appear that the criteria to be used to verify the success of these additional specialised educational materials will be annual evaluation of incidence of rash, diarrhoea and interstitial lung disease and any feedback received from prescribers regarding the educational materials. Copies of these educational materials were provided in the sponsor's submission with the EU-RMP and the Australian RMP Addendum. The Australian RMP Addendum confirms the use of these additional specialised educational materials in Australia.

OPR reviewer comment

The sponsor's proposed use of routine risk minimisation activities and the Risk Minimisation Plan (RiMP) would appear to be reasonable. However the data from spontaneous ADRs are unlikely to be sufficient in measuring the effectiveness of the proposed additional risk minimisation activities. This is due to the under-reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete.

In response the sponsor's correspondence, dated 30 March 2012, proposed to solicit feedback from an appropriate target audience (predominantly nurses since they actively manage patients on a day to day basis and are familiar with the materials) via a questionnaire at the end of the In-service presentation on an annual basis. The questionnaire will request feedback on the quality and usefulness of the materials as a means to educate and manage rash, diarrhoea and ILD. The sponsor will collate the data and assess what improvements to the educational materials, if any, are necessary. This approach would be acceptable if in addition a representative sample of patients was similarly surveyed on an annual basis in relation to the patient educational materials, and the results/analyses of these investigations provided to the TGA for review.

In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information document is considered satisfactory.

Summary of recommendations

supportive to the application; the implementation of a RMP satisfactory to the TGA was imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- Given the proposed extension of indications and the target population, there is no objection to the sponsor implementing only routine pharmacovigilance activities to monitor all the specified Ongoing Safety Concerns.
- The Ongoing Safety Concerns for which additional risk minimisation activities have not been proposed would not appear to warrant additional risk minimisation

activities. Therefore the conclusion that routine risk minimisation activities for these Ongoing Safety Concerns are sufficient was considered acceptable.

- Table 67: 'A Summary of Planned Risk Minimisation Actions' should be amended to indicate that routine risk minimisation activities are not sufficient for the Important identified risks: 'Cutaneous toxicity', 'Interstitial lung disease' and 'GI fluid loss' to be consistent with Section 6: 'Risk Minimisation Plan' of the EU-RMP, which states: "*Additional risk minimisation activities in the form of specialised educational materials for healthcare professionals and/or patients for identified ADRs (rash, diarrhoea and ILD) have been prepared to anticipate and manage these specific ADRs.*"
- The sponsor's proposed use of routine risk minimisation activities and the Risk Minimisation Plan (RiMP) would appear to be reasonable. However the data from spontaneous ADRs are unlikely to be sufficient in measuring the effectiveness of the proposed additional risk minimisation activities. In response the sponsor's correspondence, dated 30 March 2012, proposed to solicit feedback from an appropriate target audience (predominantly nurses since they actively manage patients on a day to day basis and are familiar with the materials) via a questionnaire at the end of the In-service presentation on an annual basis. The questionnaire will request feedback on the quality and usefulness of the materials as a means to educate and manage rash, diarrhoea and ILD. The sponsor will collate the data and assess what improvements to the educational materials, if any, are necessary. This approach would be acceptable if in addition a representative sample of patients was similarly surveyed on an annual basis in relation to the patient educational materials and the results/analyses of these investigations provided to the TGA for review.
- In regard to the proposed routine risk minimisation activities, the draft product information document was considered satisfactory.
- In regard to the proposed routine risk minimisation activities, the draft consumer medicine information document was considered satisfactory.

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 a submission of this type.

Nonclinical

Three literature references of Erlotinib activity on EGFR mutants were evaluated. Nineteen EGFR mutants were examined and 14 were found to be oncogenic ('activating'). Erlotinib inhibited cell proliferation associated with 12 of the 14 oncogenic mutants.

The sponsor was asked to comment on the validity of the test in detecting oncogenic mutations.

Clinical

Following oral administration, Erlotinib is absorbed at a moderate rate (mean time of peak plasma concentration (C_{max}) 4 h), extensively metabolised and slowly eliminated (median half life ($t_{½}$) 36 h). The mean absolute bioavailability is 59% in healthy volunteers.

Gastrointestinal and dermatological adverse effects are common. Serious effects include interstitial lung disease, hepatitis, diarrhea, gastrointestinal perforation and skin disorders.

Efficacy

- The pivotal efficacy study was a randomised, open-label, parallel-group trial (ML20650 or EURTAC) in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) with activating EGFR mutations who had not previously received chemotherapy for advanced disease. Patients received either Erlotinib 150 mg orally once daily or a standard platinum-based doublet chemotherapy regimen (cisplatin or carboplatin with docetaxel or gemcitabine intravenously in 3 week cycles). The treatments were given until disease progression or unacceptable toxicity (or in the case of chemotherapy a maximum of 4 cycles). Most patients were female (68% on Erlotinib and 79% on chemotherapy) and the median age was 65 years (range 24-82).
- The primary endpoint was investigator-assessed progression free survival (PFS). In the planned interim analysis at cut-off 2 August 2010, Erlotinib significantly increased PFS compared with chemotherapy by a median 4.2 months (Table 17). The result was confirmed in Cox regression adjusting for covariates and independent review. The tumour response was also significantly greater with Erlotinib. Overall survival data were immature. The median follow-up for Erlotinib and chemotherapy patients was 14 and 11 months respectively.
- Following review of the interim results by the independent data monitoring committee, further trial recruitment was ceased on 24 January 2011. An updated analysis at that time was consistent with the initial analysis and has been published in *Lancet Oncology*[6].

Table 17. ML20650 Trial – Efficacy Results – *Interim – Intent-to-Treat*

	Erlotinib PO 150 mg daily n=77	Chemotherapy IV q3w n=76	Hazard Ratio or Difference [95% CI]
PFS - *investigator*[1,2] median *mths*	9.4	5.2	0.42 [0.27, 0.64]
PFS – *independent*[1] median *mths*	10.4	5.4	0.47 [0.27, 0.78]
Overall Survival[1] median *mths*	22.9	18.8	0.80 [0.47, 1.37]
Overall Response Rate[2] *%*	54.5	10.5	44.0 [30.2, 57.9]

[1] Medians are Kaplan-Meier estimates and Hazard Ratios are Cox regression estimates (Erlotinib/chemotherapy). [2] Investigator-assessed using RECIST criteria.

[6] Rosell R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239-46.

- Updated data from the previously evaluated first-line maintenance trial BO18192 (also known as SATURN) were supportive of the efficacy of Erlotinib in subjects with advanced NSCLC with activating EGFR mutations. The updated PFS (additional 5 months to 17 May 2009) and overall survival (to February 2011) were consistent with the previous analysis. The overall survival data were immature. The data in the subgroup of patients with activating EGFR mutations showed that the benefits of Erlotinib were more evident in this group than in the overall trial population.

Safety

- The safety population were patients from the pivotal ML20650 trial receiving at least one dose of study medication; 84 Erlotinib and 83 chemotherapy patients (updated analysis). The median duration of treatment was 9.3 months on Erlotinib and 2.5 months on chemotherapy. Adverse events were consistent with known safety profiles. Diarrhoea, mucosal inflammation, cough, dyspnoea, skin and musculoskeletal disorders, paronychia and conjunctivitis were more common with Erlotinib than chemotherapy.
- The incidence of serious adverse events was similar for Erlotinib and chemotherapy; 31% each in the updated analysis. The incidence of events leading to treatment withdrawal was also similar, 12% for Erlotinib and 15% for chemotherapy, based on the primary analysis. There were no data for the updated analysis. Dose modification and interruption was less frequent with Erlotinib; 27% Erlotinib versus 52% with chemotherapy also based on the primary analysis. Most of the chemotherapy dose modifications were due to haematological toxicity. There were 8 deaths due to adverse events with Erlotinib and 4 with chemotherapy. The Erlotinib deaths included deaths due to hepatotoxicity and interstitial lung disease.

The evaluator recommended approval of the new indication.

Risk management plan

- The RMP proposed is the EU RMP version 3.1, dated July 2011, and an Australian Addendum version 1.0, dated 2 September 2011. This was acceptable to the TGA Office of Product Review.

Risk-benefit analysis

Delegate considerations

In first-line treatment of patients with advanced NSCLC with activating EGFR mutations, Erlotinib significantly increased PFS by a median 4.2 months compared with standard chemotherapy (trial ML20650). There was a trend to increased overall survival (median 4.1 months increase). An updated analysis of overall survival will be available in the fourth quarter of this year (sponsor's letter of *response* 30 March 2012). Data from the EGFR mutation-positive subgroup of a first-line maintenance trial (BO18192) were supportive.

The adverse event profile of Erlotinib was consistent with previous experience.

A side issue is the appropriateness of the broad existing NSCLC indications. The benefits of Erlotinib appear to be confined to patients with tumours with activating EGFR mutations. The *Lancet Oncology* paper of the first-line trial interprets the findings as applying more generally to patients with NSCLC. Further, available data for the EGFR IHC +ve and –ve subgroups and patients with activating EGFR mutations from the maintenance and second to third-line trials point to the benefits of Erlotinib being limited to patients with

activating EGFR mutations. The Delegate recommends all patients with NSCLC be tested for EGFR mutations before commencement of Erlotinib. The Delegate also recommended a qualifying statement under *Indications* in the product information and inclusion of results for patients with activating EGFR mutations and EGFR IHC +ve and –ve subgroups from the trials supporting the maintenance and second to third-line indications. This is consistent with the European product information.

Delegate's draft decision

The Delegate recommended approval of Erlotinib (Tarceva) for the indication proposed:

> *First-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.*

The Delegate also recommended the following qualifying statement under the maintenance and second- to third-line indications in the product information:

"*In patients with EGFR-IHC negative tumours, Tarceva has not demonstrated clinically relevant survival or other benefits* (see *Clinical Trials*)"

and additional information under *Clinical Trials* the details of which is beyond the scope of this AusPAR.

Approval should be subject to finalisation of the product information.

Proposed conditions of registration:

- Implementation of the EU Risk Management Plan version 3.1, dated July 2011, and Australian Addendum version 1.0, dated 2 September 2011, and subsequent revisions as agreed with the Office of Product Review.
- Submission of updated survival data from trial ML20650 when available.

Submitted to the Advisory Committee on Prescription Medicines (ACPM) for advice.

Response from sponsor

References cited by numbers in the sponsor's response have been listed at the end of the section.

Summary of the Delegate's recommendations and the sponsor's response

The sponsor concurs with the Delegate's recommendation to approve Tarceva (Erlotinib) 25 mg, 100 mg and 150 mg film coated tablets for the following indication:

> *"Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations."*

The sponsor does not concur with the Delegate's proposal to include the following additional qualifying statement in the indications section, as per the European labelling for Tarceva (TAR):

> *"In patients with EGFR-IHC negative tumours, Tarceva has not demonstrated clinically relevant survival or other benefits (see Clinical Trials)".*

The sponsor believes the Delegate's intent in proposing this statement is part of the larger package of PI changes to confine TAR use to patients with tumours harbouring activating Epidermal Growth Factor Receptor (EGFR) mutations. The sponsor disagrees with this conclusion. TAR demonstrates benefit in patients with tumours of the EGFR wild-type (EGFRwt) genotype in maintenance and second lines of therapy and in patients with tumours of the EGFR activating mutation (EGFRmut+ve) genotype across all treatment

lines. The sponsor also disagrees that the above EU statement would assist with confining TAR use to patients with EGFRmut+ve tumours. EGFR-IHC negative status (EGFR-IHC -ve) should not be read to indicate an EGFR activating mutation negative genotype (that is, EGFRwt), and EGFR-IHC –ve is not considered a reliable test for selecting responders to EGFR targeted therapy.

The sponsor believes including this statement in the *Indications* will be confusing and potentially misleading to the reader. Confusing because the reader may mistake EGFR-IHC –ve status to equate to a negative status for activating mutations and misleading because it suggests an EGFR-IHC –ve status is a reliable means to select responding patients. Either situation could result in a patient not receiving a medication which could otherwise benefit them. Consequently the sponsor also does not concur with the PI changes under *Clinical Trials* recommended by the Delegate and which are related to the proposed indication statement above.

The sponsor does concur with the Delegate's proposed conditions of registration, as listed in the Delegate's Overview.

The following discussion refers to 2 Phase III studies previously evaluated by the TGA. The BR.21 study was the subject of a previous application approved 13 January 2006 and BO18192 (the SATURN study) was the subject of an application approved via appeal 9 September 2010. BR.21 and SATURN were the pivotal trials supporting registration of the second-line indication and first-line maintenance indications, respectively, in Australia, the USA, Europe, Canada and many other countries around the world. Updated subgroup data from SATURN (SATURN CSR Addendum Report No. 1033732, August 2009) was included in the dossier for this submission to support the findings from the pivotal EURTAC study. Report 1033732 was also previously submitted to the TGA as part of a previous submission.

EGFR and Tyrosine Kinase Inhibitors

EGFR is one of several signalling pathways that tumours rely on for growth and spread (1). EGFR is overexpressed by up to 80% of NSCLC tumours causing abnormal activation of signalling pathways (2, 3). EGFR overexpression is associated with aggressive disease and poor survival (2, 4). TAR is a Tyrosine Kinase Inhibitor (TKI) that targets EGFR. The active ingredient, Erlotinib, competes with ATP for binding in the tyrosine kinase domain of the receptor, thereby inhibiting the EGFR signalling cascade (2). There are important differences between EGFRwt tumours and EGFRmut+ve tumours. In EGFRwt tumours, the EGFR pathways play an important role in regulating cell survival and proliferation, although additional cell signalling pathways are also believed to be active (2, 3). EGFRmut+ve tumours are hyper-dependent on the EGFR pathway, leaving other pathways redundant and making EGFR even more critical to the development of NSCLC (3).

EGFR as a Biomarker - Tumour Screening and Classification by Immunohistochemical Staining (IHC) or Mutation Status

Biomarker analysis of tissue samples from NSCLC tumours (both primary and metastatic tumours) can be undertaken using a variety of techniques. Which technique is chosen depends on the nature of the biomarker of interest and the information sought. EGFR-IHC staining assesses the degree of expression of the EGFR protein whilst mutations in the protein are assessed by a variety of DNA analysing technologies.

The EGFR IHC test consists of staining a tumour sample with a dye-linked antibody directed against EGFR, with the number of stained cells counted under a microscope. An arbitrary threshold of 10% membrane staining is set. If the number of stained cells is below 10% then the tumour sample is classified as EGFR-IHC –ve. If the figure is over 10% then the sample is EGFR-IHC positive (EGFR-IHC+ve). This technique is only a measure of the relative presence or absence of the EGFR protein, not if the EGFR protein is "active". By

contrast, the genotype of a tumour (that is, EGFRwt or EGFRmut+ve) is assessed via a variety of DNA analysing techniques. Assessing the EGFR mutation status provides information about whether the protein is constitutively active (in the case of EGFRmut+ve) or needs to be activated by the binding of an EGF ligand (in case of an EGFRwt). There are a number of EGFRmut+ve subtypes, the most common being the exon 21 L858R point mutation and the in-frame deletion mutation of exon 19.

Both IHC staining and DNA analysis are forms of biomarker analysis however they are independent of each other in the sense that one test does not inform about the results which could be expected in the other. If a tumour sample is classed as EGFR-IHC –ve it does not inform of the tumour's genotype, that is EGFRwt or EGFRmut+ve. And vice versa, if a tumour sample is classed as EGFR-IHC+ve it does not mean the tumour harbours an activating mutation. Given that the prevalence of activating mutations is estimated to between 10-26% in the NSCLC population, a proportion of tumour samples classified as EGFR-IHC –ve are likely to harbour activating mutations, whilst the majority of EGFR-IHC+ve tumours are likely to be EGFRwt.

Given this situation the sponsor believes that the identification of responders to treatment with TAR cannot rely on IHC status. Initial assessments of EGFR expression by IHC as a biomarker for EGFR TKIs suggested the possibility that this technique could be developed to discriminate between responders and non-responders (5, 6). However, with the refinement of the technology the proportion of patients with EGFR-IHC –ve status has decreased and any trends for differences have become gradually less pronounced. This has been observed in subsequent studies with EGFR targeted therapies [7-12].

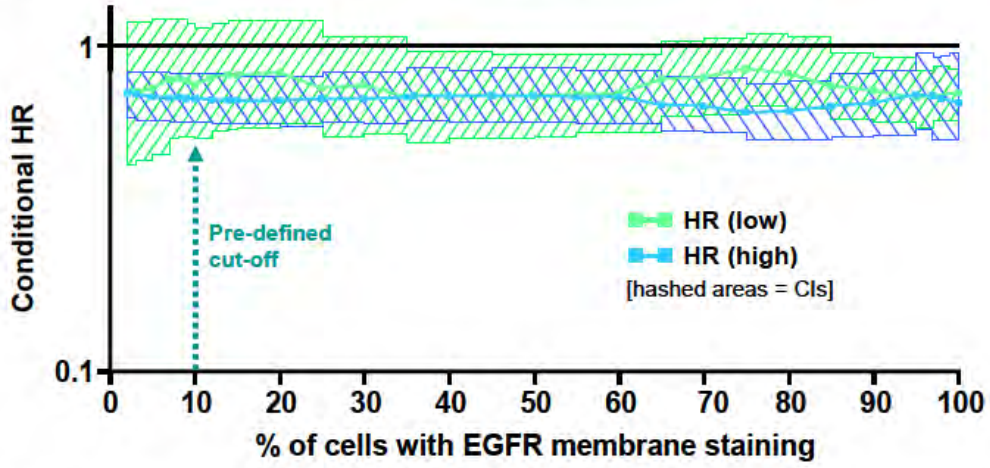
EGFR-IHC Status is not a Reliable Method to Select Patients – SATURN As An Example

Despite the lack of statistical power for the EGFR-IHC –ve subgroup in SATURN the sponsor believes there is a suggestion of clinical benefit in this subgroup. The magnitude of PFS benefit observed in the EGFR-IHC –ve population is similar to the benefit observed in the overall population (HR=0.77 [0.51; 1.14] versus HR=0.71 [0.62; 0.82], respectively). However, due to the small sample size in the subgroup, statistical significance cannot be shown. Fifty-nine and 62 patients were EGFR-IHC –ve in the placebo and Erlotinib arms respectively, so there is only approximately 26% power to show a significant result with a HR of 0.77.

The possibility of an efficacy benefit in patients with tumours classified as EGFR-IHC –ve is biologically plausible and logical. Both healthy cells and NSCLC tumour cells express EGFR in their membranes. The TKI inhibition of the EGFR signalling pathway is active independent of the level of EGFR expression on NSCLC tumour cell surfaces. EGFR-IHC status is defined only by the level of EGFR protein on the cell surfaces of the tumour cells. An arbitrary figure of 10% cellular staining was set as the cut-off. To assess if there was a more appropriate threshold of expression that could clearly separate responders from non-responders, a Cox Regression analysis for different IHC cut-offs was performed (Figure 11). Regardless of where the predefined cut-off for percentage of stained cells is set (0 to 100%), the HR for EGFR-IHC+ve and EGFR-IHC –ve patients consistently remains below 1 with little difference between HR for EGFR-IHC+ve and EGFR-IHC –ve patients. Therefore the sponsor believes it is not possible to identify an optimised cut-off, further highlighting that EGFR protein expression by IHC is not a suitable biomarker. Further confirmation is derived from an interaction test which demonstrated no correlation between IHC status and PFS (p=0.6579) or overall survival (OS) (p=0.5238). Thus there is no correlation between anti-tumour activity and EGFR protein expression. The published consensus is that EGFR-IHC status is not a reliable test for selection of responders to EGFR targeted therapy in NSCLC [13-15]. A number of reasons for this have been suggested, including EGFR expression in NSCLC tumours is very heterogeneous [16], making a robust assessment of the true EGFR-IHC status of the tumour difficult, and the discordance rates

in EGFR-IHC status between primary and metastatic tumours has been reported to be as high as 33% in NSCLC [17].

Figure11. Cox regression for different IHC cut-offs (any membrane staining).



(Hashed areas represent 95% CI at each cut-off. Population quartiles were: 25% of patients with up to 35% stained cells, 25% of patients with between 35% and 90% stained cells, 25% of patients with between 90% and 100% stained cells and 25% of patients with 100% stained cell. Therefore, 50% of patients had at least 90% stained cells.)

In the EGFR-IHC –ve subgroup in SATURN (n=121) the EGFR mutational status was determined for 64 patients (9 mutants and 55 wild-type). Of the 9 patients confirmed as having EGFRmut+ve tumours 5 received TAR, and of these 3 were among the longest surviving patients in the EGFR-IHC –ve subgroup. Three patients had OS durations of 28 months, 24 months, and 23 months, respectively. This further highlights the lack of reliability of EGFR protein expression as a predictive marker. When the clinical benefit analysis was limited to the 55 EGFRwt patients, the PFS and OS HR were 0.66 [0.36; 1.20] and 0.64 [0.35; 1.20], respectively, demonstrating that the benefit observed in the EGFR-IHC –ve patients is not exclusively driven by patients with EGFRmut+ve tumours.

In conclusion, the sponsor believes that EGFR protein expression by IHC is not an appropriate marker to distinguish responders from non-responders in NSCLC. Including the additional statement in the *Indications* would most likely have the unintended consequence of excluding some EGFR-IHC –ve status patients from treatment, so denying them a treatment from which they would benefit. This situation applies to EGFR-IHC –ve patients across all lines of therapy. The sponsor does conclude however that EGFR genotype (EGFRwt or EGFRmut+ve) is an appropriate biomarker to guide NSCLC treatment in the *first-line* setting, as demonstrated by the results from the EURTAC study.

Tarceva efficacy in EGFRwt and EGFRmut+ve tumours

The Delegate concludes "*the benefits of Erlotinib appear to be confined to patients with tumours with activating EGFR mutations*." The sponsor believes this conclusion to be incorrect since the data from BR.21 and SATURN demonstrate TAR is efficacious in tumours of the EGFRwt genotype. The sponsor acknowledges that the efficacy benefit is greatest in patients who are EGFRmut+ve; however an efficacy benefit has also been demonstrated in patients with EGFRwt tumours. The Delegate also comments that the "*Lancet Oncology paper [Rosell R et al. 2012] of the first-line trial interprets the findings as applying more generally to patients with NSCLC*." The sponsor agrees the paper recommends routine tissue-based screening of all NSCLC patients, but the sponsor contends this is to guide appropriate *first-line* treatment (TKI or standard chemotherapy depending on tumour EGFR genotype). There is no suggestion in the paper that the

authors are questioning the benefit of TAR as a therapeutic option in later lines of treatment.

Nonlinical Data

Based on nonclinical studies both EGFRwt and EGFRmut+ve tumour types are thought to be dependent on EGFR for cell survival and proliferation and both tumour types are sensitive to TAR although to different levels. Furthermore, despite the fact that both *Erlotinib* and another TKI, *gefitinib*, target EGFR, nonclinical (and clinical data) have highlighted important differences between the two. A key difference believed to underlie the different clinical observations with the two compounds is that whereas *gefitinib* is unable to achieve sufficient plasma concentrations to effectively inhibit both EGFRwt and EGFRmut+ve, this concentration is reached with *Erlotinib* with standard dosing [18-20].

Clinical Data

TAR was shown to be effective in the registration studies SATURN and in BR.21. Both studies enrolled a mixed population, including patients with NSCLC with either EGFRwt or EGFRmut+ve tumours.

SATURN (co-primary endpoints: PFS in all patients and PFS in the EGFR-IHC+ve population)

Patients with EGFRmut+ve (49 patients, 27 placebo and 22 on TAR) and EGFRwt tumours (388 patients, 189 placebo and 199 on TAR) derived significant benefit from treatment with TAR, demonstrated by the PFS HRs of 0.10 [0.04; 0.25] (p<0.0001) and 0.78 [0.63; 0.96] (p=0.0185), respectively, suggesting that the benefit in the ITT population (PFS HR of 0.71 [0.62-0.82] (p<0.0001)) was not driven by the EGFRmut+ve subset. In the updated analysis included with this submission (and submitted with a previous application) the PFS benefit from treatment with TAR in the EGFRmut+ve subgroup remained highly significant at the cut-off date (17 May 2009), HR 0.23 [0.12; 0.45], p < 0.0001. Efficacy benefit was also maintained in the EGFRwt subgroup (HR 0.78 [0.64; 0.96], p=0.0182), almost identical to those at the CSR data cut-off (17 May 2008) shown above. In the updated analysis for OS (17 May 2009 cut-off), data in the EGFRmut+ve subgroup was still immature, in particular in the TAR arm (only 8 patients out of 22 had died at the time of cut-off). Median OS was not reached in the TAR arm (Table 18). Patients with EGFRwt tumours had longer survival with TAR treatment compared to placebo as demonstrated by an HR of 0.77 [0.61; 0.97] (p=0.0243, Table 19), suggesting that the benefit in OS in the ITT population (HR=0.81 [0.70-0.95], p-value=0.0088, reported in the TAR PI) was not driven by the EGFRmut+ve subset.

Table 18. Summary of OS in the EGFR mutation positive subgroup (SATURN study; data cut-off 17 May 2009).

	PLACEBO (N=27)		ERLOTINIB (N=22)
Patients with event	13 (48.1 %)		8 (36.4 %)
Patients without event*	14 (51.9 %)		14 (63.6 %)
Time to event (months)			
Median#	23.8		.
95% CI for Median#	[17.5;.]		[16.8;.]
25% and 75%-ile	14.9;.		15.4;.
Range##	5.1 to 31.9		4.7 to 30.4
p-Value (Log-Rank Test)		0.6810	
Hazard Ratio		0.83	
95% CI		[0.34;2.02]	
1 year estimate			
Patients remaining at risk	22		17
Event Free Rate#	0.81		0.77
95% CI for Rate#	[0.67;0.96]		[0.60;0.95]

Survival [months] (TTDIED_M) - Censoring: Death Censoring (1=death, 0=censored) (CSDIED)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2009

Table 19. Summary of OS in the EGFR wild type subgroup (SATURN study; data cut-off 17 May 2009).

	PLACEBO (N=189)		ERLOTINIB (N=199)
Patients with event	152 (80.4 %)		142 (71.4 %)
Patients without event*	37 (19.6 %)		57 (28.6 %)
Time to event (months)			
Median#	10.2		11.3
95% CI for Median#	[8.9;11.7]		[9.5;14.3]
25% and 75%-ile	5.8;17.2		6.1;21.7
Range##	0.0 to 32.3		0.3 to 31.3
p-Value (Log-Rank Test)		0.0243	
Hazard Ratio		0.77	
95% CI		[0.61;0.97]	
1 year estimate			
Patients remaining at risk	75		91
Event Free Rate#	0.41		0.49
95% CI for Rate#	[0.34;0.49]		[0.42;0.56]

Survival [months] (TTDIED_M) - Censoring: Death Censoring (1=death, 0=censored) (CSDIED)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2009

BR.21 (primary endpoint: OS)

The benefit in OS in the ITT population (731 patients) was HR=0.70 [0.58 to 0.85], p-value <0.001. In the subset of patients with EGFRwt tumours or mutations other than exon19 deletion or exon 21 L858R mutation (170 patients) HR = 0.74 [0.52 to 1.05]. In the subset of patients with exon19 deletion or exon 21 L858R mutations (34 patients) HR = 0.55 [0.25 to1.19] [21]. The HRs suggest an efficacy benefit in both subsets however the study was not powered for this purpose.

Qualifying statement in the EU label

It is not the intention of the qualifying statement in the EU labelling to confine TAR use to only patients with EGFRmut+ve tumours, which the sponsor understands is the Delegate's intended purpose of proposing its inclusion in the PI. Indeed the first-line maintenance and second/third line indications in the current EU label are not restricted to only patients with EGFRmut+ve tumours since EGFR mutation testing is only recommended for *chemo-naïve* patients. EGFRwt patients remain eligible to receive TAR as maintenance or after failure of a prior chemotherapy regimen.

The indication statement and the corresponding EGFR-expression status data have been included in the EU labelling since EU registration of TAR in 2005. Its purpose was to inform the reader of the subgroup data from the pivotal registration trial BR.21. At the time of EU registration initial assessments considered that *EGFR-negative status* (that is, EGFR-IHC –ve status, not EGFR activating mutation "negative"; the terminology has evolved since 2005) could be a biomarker for EGFR TKIs and there was the possibility that the IHC technique could be developed to discriminate between responders and non-responders. However the general consensus now is that EGFR protein expression as measured by IHC is not an appropriate marker to distinguish responders from non-responders in NSCLC. More recently the EU label has been revised slightly to "*No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-IHC negative tumours (see section 5.1)*" in an attempt to avoid confusion between EGFR-IHC+ve or EGFR-IHC -ve patients and EGFRmut+ve or EGFRwt patients. The intent being to clarify that the previous broad EGFR-negative status was in fact just referring to EGFR-IHC -ve not an absence of an activating mutation. The revised wording was accepted by the EMA.

TGA were informed of the EU indication and the EGFR-expression status data as part of the sponsor's pre-ACPM response considered at the December 2005 Austrlaian Drug

Evaluation Committee (ADEC; now called ACPM) meeting. At the time TGA did not request inclusion of the qualifying statement or the subgroup data in the PI.

The sponsor contends including the proposed statement in the Australian PI will create confusion rather than add clarity. Its appearance would coincide with inclusion of the proposed first-line indication suggesting a link between the two. As previously described, EGFR-IHC –ve status does not equate to a negative status for activating mutations and EGFR-IHC –ve status is not a reliable means to select responding patients.

Response to the Delegate's request for "Sponsor comment on the validity of the test in detecting oncogenic mutations"

This question was asked in relation to the Nonclinical Evaluation commentary in the Delegate's Overview. In response, the sponsor provides comment on the detection of the mutations in the 3 literature references quoted and on EGFR mutation testing in Australia.

Literature references

In the three literature references quoted the EGFR mutations were cloned into the cell-lines [18, 22], and the transgenic mouse model [23]. Confirmation of the presence of the EGFR mutations was either via sequencing [18, 22] or PCR [23].

Mutation tests available in Australia

There are several analytical techniques that can be used to establish the presence of an EGFR mutation in a tumour sample. These techniques can be divided into those that sequence a length of DNA to screen for unknown mutations (normally for research purposes) and those that analyse a specific nucleotide to identify a known mutation. Various methodologies for identifying EGFR mutations are used and often include PCR amplification of the DNA of interest, followed by mutation detection. A list of EGFR tests available in Australia to determine EGFR mutation status is presented in Table 20. Sanger sequencing is a common choice.

Table 20. EGFR mutation rests available in Australia

Test	Test kit/antibody or DNA probe name	Sponsor/local supplier	ARTG number	Approved indication
cobas® EGFR Mutation Test	EGFR Mutation Test. TAQMAN Real-Time PCR	Roche Diagnostics, Australia	194319 Class 3	To identify patients with advanced NSCLC whose tumours harbour mutations in exons 18, 19, 20 and 21 of the EGFR gene, and to select patients for treatment with small-molecule tyrosine kinase inhibitors (TKIs) that target EGFR. Specimens are processed using the cobas® DNA Sample Preparation Kit for manual sample preparation and the cobas z 480 analyser for automated amplification and detection.
Direct DNA Sequencing	Di-deoxy capillary sequencing or Sanger sequencing	Laboratory manufactured test	–	–
High resolution melting (HRM)	Gene scanning via real time PCR. Melting curve analysis.	Laboratory manufactured test	–	–
DxS TheraScreen EGFR29 Mutation Test	PCR-based assay. ARMS primers and Scorpions technology	Qiagen	–	Used for research purposes only
Sequenom melacarta and oncocarta panel	MassARRAY system, single nucleotide polymorphisims (SNPs), iPLEX Pro assay	Sequenom	–	Used for research purposes only
Next Generation Sequencing - Pyrosequencing (e.g. 454 sequencing)	Sequence-based methodology	Roche Diagnostics Australia	–	Used for research purposes only

Validity of EGFR mutation tests

An assay designed for EGFR mutation testing is classified as an *in vitro* diagnostic medical device (IVD). IVDs are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management. EGFR mutation testing is a Class 3 IVD. The TGA regulatory framework for IVDs changed in July 2010. All Class 1-3 IVDs, including both commercially available kits and in-house assays (laboratory developed tests) are now required to be registered with the TGA (unless they were offered prior to July 1 2010 where a transition period up to June 2014 applies). Complementary to the IVD regulatory framework is National Association of Testing Authorities, Australia (NATA) accreditation. NATA accreditation is a standard awarded to a laboratory which satisfies the quality standards set by the National Pathology Accreditation Advisory Committee (NPAAC).

In February 2011 the Medical Services Advisory Committee (MSAC) recommended that all EGFR mutation testing should only be performed in NATA accredited laboratories. Competence to perform the test will be monitored through the RCPA Quality Assurance Program (QAP). The QAP will ensure high quality testing in all Australian laboratories and assess collection and handling methods of samples. Whilst the proposed Tarceva PI does not state which specific mutation test should be used (since different laboratories employ different methodologies), the regulatory framework in place for IVDs and the requirement for NATA accreditation ensures all EGFR mutation tests used in Australia are validated and robust.

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Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit–risk profile for the proposed new indication:

> *Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.*

In making this recommendation the ACPM agreed with the Delegate that the efficacy has been demonstrated for first line therapy where the EGFR mutation status of a patient's tumour is known. However, the ACPM advised that there is an overall lack of reliability and barriers to immunohistochemical testing of EGFR protein expression as a sole determinant of efficacy in second and third line therapy. The ACPM therefore advised that use in second and third line therapy should not be limited to EGFR mutation positive patients and therefore this stipulation should be removed from the indication, together with the supporting data highlighted in the PI.

The ACPM advised that the amendments to the Product Information (PI) and Consumer Medicine Information (CMI) should be amended to include the following:

- a statement in the Dosage and Administration and Clinical Trials section of the PI and relevant sections of the CMI to ensure the reference to reliability of genetic testing beyond first line therapy is understood by both the prescriber and consumers.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tarceva, containing Erlotinib, for the new indication:

> *For the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.*

The full indications are now:

> *Non-small cell lung cancer*:
>
> > *Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.*
> >
> > *Tarceva is indicated for maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy. Efficacy is influenced by tumour characteristics (see Clinical Trials).*
> >
> > *Tarceva is also indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.*
>
> *Pancreatic cancer:*
>
> > *Tarceva in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.*

Specific conditions applying to these therapeutic goods:

1. Implementation of the EU Risk Management Plan version 3.1, dated July 2011, and Australian Addendum version 1.0, dated 2 September 2011, and subsequent revisions as agreed with the Office of Product Review.
2. Submission of updated survival data from trial ML20650 when available.

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/hp/information-medicines-pi.htm>.

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Reference/Publication #