Australian Government

Department of Health and Ageing

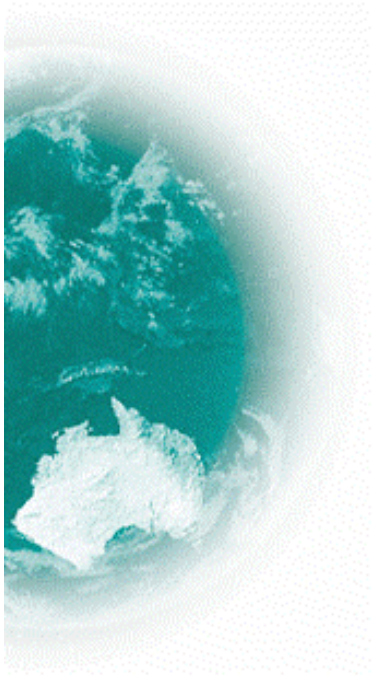
Therapeutic Goods Administration

Australian Public Assessment Report for Erlotinib

Proprietary Product Name: Tarceva

Submission No: PM-2009-00835-3-4

Sponsor: Roche Products Pty Ltd



November 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Initial Decision:	16 April 2010
Date of Final Decision:	9 September 2010
Active ingredient(s):	Erlotinib
Product Name(s):	Tarceva
Sponsor's Name and Address	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
Dose form(s):	Film coated tablet
Strength(s):	25 mg, 100 mg and 150 mg
Container(s):	Blister pack
Pack size(s):	30 tablets
Approved Therapeutic use:	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.
Route(s) of administration:	Oral
Dosage:	150 mg daily
ARTG Numbers (s):	114714, 114717, 114721

Product Background

Erlotinib (Tarceva) is an inhibitor of the epidermal growth factor receptor (EGFR). It is currently registered (as monotherapy) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of cytotoxic chemotherapy (that is, as second or third line therapy). It was registered for this indication in January 2006, following consideration by the Australian Drug Evaluation Committee (ADEC) at its December 2005 meeting. The approved dose for the current NSCLC indication is 150 mg per day.

The current application seeks approval for use as maintenance therapy after completion of first line chemotherapy. It therefore seeks to establish a role for the drug at an earlier stage in the disease process (that is, use before, as opposed to after, disease progression). The recommended dose remains 150 mg per day.

There is one other EGFR inhibitor registered in Australia for the treatment of NSCLC – gefitinib (Iressa). It has recently been approved for a limited first line indication.

Tarceva is also indicated for the treatment of pancreatic cancer:

in combination with gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic

Regulatory Status at the Time of Submission

The product received initial ARTG Registration in January 2006.

An application for the proposed new indication has been submitted to the United States (18 March 2009), the European Union (20 March 2009), Switzerland (14 May 2009) and Canada (second quarter, 2009). All were currently under evaluation at the time the evaluation of this submission.

Product Information

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

II. Quality Findings

Quality Summary and Conclusions

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

III. Non-Clinical Findings

Non-Clinical Summary and Conclusions

There was no requirement for a non-clinical assessment in an application of this type.

IV. Clinical Findings.

Introduction

This application is seeking approval for erlotinib administered as a single agent following four cycles of platinum-based chemotherapy as first line maintenance treatment for patients with locally advanced or metastatic NSCLC. The basis for this application is a single trial which was a randomised, double blind, placebo controlled Phase III study entitled BO18192 or SATURN. In this multicentred trial in patients with histologically documented advanced or recurrent stage IIIB or IV with NSCLC and who had not experienced disease progression or unacceptable toxicity during chemotherapy who were randomised following four cycles of platinum-based chemotherapy in which no evidence of disease progression occurred to receive either erlotinib or placebo. Treatment was to continue until disease progression, unacceptable toxicity or death. The primary objective for efficacy was progression free survival (PFS) with secondary objectives including overall survival (OS) and toxicity. A total of 889 patients were randomised into this trial.

Full data were provided in the submission including summary and full reports concerning population pharmacokinetics, efficacy and full safety data. All reports including relevant summaries and tables were appropriately presented and adequate for evaluation.

Post-marketing data regarding safety were also provided in the submission.

The original TGA clinical evaluation of the application was based on the sponsor's report of the trial dated March 2009. The cut-off date for inclusion of data in this report was 17 May 2008.

In response to a request from the TGA for updated data, the sponsor submitted an addendum to the original study report. The addendum report was dated August 2009 and the cut-off date for inclusion of data was 17 May 2009 (that is, an additional 12 months of follow-up).

Pharmacokinetics

The only pharmacokinetic (PK) or pharmacodynamic (PD) data provided in this submission arises in relation to study BO18192 (SATURN) in which plasma samples were collected for all randomised patients in this trial. All patients entering into the trial had five PK samples taken including one at baseline on visit Day 1 of the study before the first dose of medication, two on visit

Week 6 including one pre-dose sample and one post-dose sample, and two on visit Week 12 including one pre-dose sample and one post-dose sample. Previous population PK analyses had determined that a one compartment model with first order absorption and elimination reasonably well described the concentration/time data of the parent drug. From the previous analyses the PK parameters for the typical patient were 3.95 L/hr for clearance, 2.33 L for the erlotinib volume of distribution and 40.9 hours for the erlotinib terminal half-life. Coefficients of variation for intra-individual variability of clearance and volume of distribution were 39.4% and 71.7% respectively. The most important covariants determined in relation to clearance from the earlier studies included total bilirubin, alpha 1 acid glycoprotein and smoking status.

The previous population PK model was used to analyse the current PK data from the SATURN study. A Bayesian feedback approach was applied to the site where the existing pharmacokinetic model was able to describe the observed plasma concentrations and the function of the dosing history and demographic covariates.

Secondary parameters area under the curve (AUC) were derived from individual post-dose estimations. An exploratory PK/PD analysis was performed with the primary focus on the relationship between measures of exposure to erlotinib and drug-related adverse effects, such as skin rash and diarrhoea, with secondary focus on the relationship between parameters and exposure and clinical efficacy parameters. In addition the potential impact of the following biomarkers - EGFR fluorescence in situ hybridisation (FISH), K-ras mutation, EGFR mutation - on the safety and efficacy parameters were explored.

A total number of 308 patients were eligible for this analysis. They were treated with erlotinib and had at least one measurable plasma concentration post-dose. A total number of 882 plasma samples were measurable and erlotinib concentrations were collected.

The goodness of fit plots as well as plots superimposing the individual predictions, population predictions and the actual observations provided convincing evidence that the existing PK model was able to predict the observations reasonably well. The final model included the effect of smoking habit, gender, alpha 1 acid glycoprotein, albumin, bilirubin and creatinine clearance on apparent clearance of erlotinib. The impact of the continuous covariates appears to be small compared to the observed overall variability. In all graphs the model trend line which takes into account all the covariates as well as the smooth line to the derived estimated clearance values are approximately comparable.

Consistent with previous findings estimated clearance appeared to be slightly higher in current smokers (approximately 20%) than those who had never smoked. The pharmacokinetic results from this study are generally consistent with previous results.

By means of the derived exposure measures earlier described, the graphical analysis of a potential relationship between exposure to erlotinib and selected parameters of safety and efficacy was performed. Parameters of safety included rash and diarrhoea as the known most common adverse events related to erlotinib.

The range of exposure values observed across the different categories of rash and including those patients who did not develop rash appear to be similar. High grades of rash appeared to be associated with higher exposure to erlotinib. However at all rash grades the range of exposure overlaps with the exposure range observed in patients without rash. The data for diarrhoea were very similar to those observed for patients with rash.

The predictive value of exposure to erlotinib for PFS, OS and best response was expressed graphically. The relationship between exposure to erlotinib and efficacy measures could not be elucidated. However efficacy in the erlotinib group was observed irrespective of the level of exposure to erlotinib. The subgroup analysis in relation to selected patient populations of special interest within the EGFR wild-type patients and the K-ras mutated patients and smoking habits

failed to reveal that any subgroup was more responsive to treatment and therefore to draw any conclusions. No correlation between biomarker status, exposure and efficacy could be elucidated.

Efficacy

Study BO18192

Earlier studies had demonstrated that erlotinib monotherapy in a second and third line setting provided a statistically significant and clinically meaningful prolongation of overall survival (OS) and progression free survival (PFS) in patients with advanced NSCLC. It was also considered that the pro-apoptotic effects of erlotinib could be beneficial when trying to enhance the anti-tumour effects of chemotherapy. A pre-clinical study in the NSCLC cell line K-caul 1 showed that sequential administration of a chemotherapy agent (docetaxel) followed by erlotinib resulted in a greater level of apoptosis compared with docetaxel alone. Although there was no significant difference in OS for erlotinib administered with concomitant chemotherapy in the first line setting in earlier studies, further exploratory analysis of the data from these studies showed that patients treated with erlotinib for more than 150 days, that is, beyond the initial four cycles of chemotherapy, showed increased response duration compared with placebo. This suggested a possible benefit for single agent erlotinib as first line maintenance therapy following chemotherapy as treatment for advanced NSCLC. Study BO18192 or SATURN was therefore designed to investigate the efficacy and safety of erlotinib compared with placebo in the maintenance setting following successful (that is, in the absence of disease progression or unacceptable toxicity) first line platinum-based chemotherapy in advanced NSCLC. It was also designed to investigate whether particular benefit was observed in patients over-expressing the endothelial growth factor receptor (EGFR). The study also assessed the benefit in this sub-population as a co-primary endpoint.

The study comprised two components, (1) Initial screening followed by first line platinum-based combination chemotherapy conducted prior to randomisation followed by (2) Study drug treatment of blinded erlotinib or placebo.

All patients included in the study were required to provide a tumour tissue sample prior to commencing chemotherapy so that EGFR protein expression status determined by immunohistochemistry (IHC) prior to randomisation of the patient into the study. Patients were then required to successfully complete four cycles of an accepted standard of platinum-based chemotherapy combination in the absence of unacceptable toxicity and/or disease progression. Patients without progressive disease after four cycles of platinum-based chemotherapy were randomised to the study if they met study eligibility criteria. Treatment was to continue until disease progression, unacceptable toxicity or death.

There were two co-primary objectives for this study:

1. To determine if administration of erlotinib in the maintenance phase after standard platinum-based chemotherapy in the treatment of NSCLC results in improved progression free survival (PFS) when compared with placebo in the overall population.
2. To determine if administration of erlotinib in the maintenance phase after standard platinum-based chemotherapy in the treatment of NSCLC results in improved PFS when compared with placebo in patients whose tumours are EGFR protein expression-positive as assessed by IHC.

Several secondary objectives were defined:

1. To compare overall survival (OS) between the two treatment arms for all patients and for patients whose tumours are EGFR protein expression-positive.
2. To compare PFS between two treatment arms in patients whose tumours were EGFR protein expression-negative.

3. To compare OS between the two treatment arms for patients whose tumours were EGFR protein expression-negative.
4. To perform exploratory evaluations of tumour tissue and blood samples for biological or genomic determinants of outcome including EGFR and K-ras mutational status and EGFR and HER2 expression status and of other molecules involved in signal transduction pathway.
5. To compare time to symptom progression between the two treatment arms.
6. To evaluate the safety profile of administering erlotinib after standard platinum-based chemotherapy in the treatment of NSCLC.
7. To investigate by a population analysis the pharmacokinetics of erlotinib including the influence of co-variates and provide post-dose estimates of exposure.

The target population of this study comprised patients with histologically documented locally advanced or recurrent stage IIIB or stage IV NSCLC. Key inclusion criteria applied to the chemotherapy run-in period included the provision to the sponsor of a tumour tissue sample. The presence of measurable disease and Eastern Cooperative Oncology Group (ECOG) status was 0-1.[1] Patients were then required to complete four cycles of acceptable standard platinum-based chemotherapy without progression of disease.

After completion of four cycles of platinum-based combination chemotherapy without disease progression patients were eligible for randomisation in a 1:1 ratio to receive either placebo or erlotinib 150 mg per day. Randomisation was stratified using an adaptive method (minimisation) that ensured a balance between the treatment arms for the following factors:

1. EGFR protein expression.
2. Stage of disease at start of chemotherapy
3. ECOG performance status
4. Chemotherapy regimen
5. Smoking status
6. Region (that is, North America, South America, Western Europe, Eastern Europe, South East Asia and Africa).

Study assessments prior to randomisation included determination of EGFR protein expression status by IHC on a histological tumour specimen previously submitted. The scheduled clinical assessments were every six weeks during treatment and after 48 weeks of treatment without disease progression every 12 weeks. Tumour response was evaluated according to the RECIST criteria.[2]

---

[1] 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

[2] RECIST criteria offer a simplified, conservative, extraction of imaging data for wide application in clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and registers four response categories:

- CR (complete response) = disappearance of all target lesions
- PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
- PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
- SD (stable disease) = small changes that do not meet above criteria

Apart from clinical tumour assessments, computed axial tomography (CT) and magnetic resonance imaging (MRI) assessments were utilised. All tumour responses were confirmed a minimum of four weeks after the initial response was noted. All responses prior to randomisation were assessed and approved by a central review.

Diagnosis of disease progression was made on the basis of increase in target lesions according to RECIST criteria or unequivocal increase in non-target disease or new lesions.

Various biomarker analyses on patients' blood or tumour specimens were performed to identify predictive indicators of clinical benefit from erlotinib therapy. This included EGFR protein expression levels, EGFR gene copy numbers, polymorphism in EGFR INTRON 1, EGFR mutation status and K-ras mutation status.

Quality of life assessments were also undertaken utilising disease related lung cancer symptoms as assessed by the Functional Assessment of Cancer Therapy – Lung (FACT-L) Version 4 questionnaire. The questionnaire was given to patients at baseline, every six weeks until Week 48 and every 12 weeks thereafter.

The primary efficacy parameter (PFS) was defined as the time from randomisation to disease progression or death which ever occurred first. Disease progression was defined according to RECIST criteria. Both the investigator and a central review panel determined response and data of disease progression. However the assessment by investigators defined the basis for the primary efficacy endpoints. The analysis of PFS was to be performed after 731 events (patients with disease progression or death) had occurred. The primary evaluation was done for all randomised patients as well as for the subset of patients with EGFR-positive tumours. The study was to be declared positive if either or both of the primary analyses were statistically significant at their pre-specified significance level. For the analysis of the overall population the significance level was 3%. For the analysis of the subgroup of patients with EGFR-positive tumours the significance level was 2%. Overall the study had a 5% significance level. Following the interim analysis the significance levels to be used for the final analysis were 0.02934 for the full analysis set and 0.01967 for the EGFR-positive subset.

The main analysis of survival was to be performed after 631 deaths had occurred which is beyond the cut-off date for this trial submission. A preliminary analysis of OS based on same data cut-off date as for the primary analysis of PFS (17 May 2008) was performed and provided in this submission. Analysis was performed for all randomised patients, patients whose tumours were EGFR protein expression-positive and those whose tumours were EGFR protein expression-negative. Responses according to RECIST criteria were complete response (CR), partial response (PR) and stable disease.

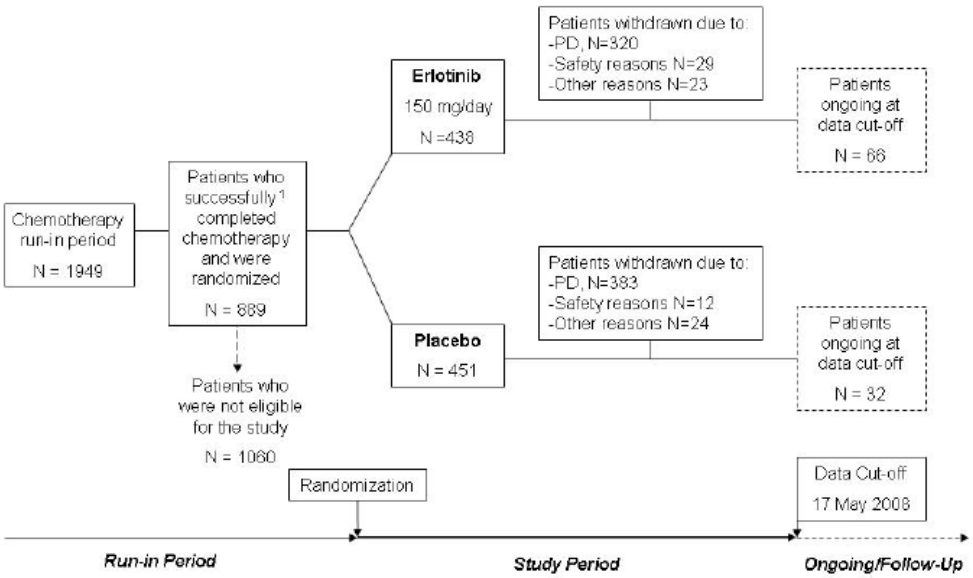
Log rank and Kaplan-Meier analyses were used for PFS and OS analyses.

A total of 1949 patients entered the chemotherapy period. Of these 889 subsequently were randomised to receive either erlotinib 150 mg per day (438 patients) or placebo (451 patients) after having completed four cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or progressive disease (Figure 1). At the time of data cut-off on 17 May 2008 after 749 events of progression or death, 98 patients were still on the study drug.

Patients were recruited by 110 centres in 26 countries. All randomised patients were included in the intent to treat (ITT) patient population. Similar numbers of patients were excluded from the per protocol (PP) population in the placebo and the erlotinib groups, 17 and 19 respectively. The treatment groups were well balanced with respect to general demographic characteristics. The study population was predominantly male and Caucasian with approximately 15% of patients being of Asian origin. The median age of patients for randomisation was approximately 60 years with an overall age range of 30-83 years. Approximately two thirds of all patients enrolled in the study had ECOG performance status of 1 and the remaining one third had ECOG performance status 0. The

majority of patients (55%) were current smokers. The groups were well balanced with respect to smoking status. The treatment groups were also well balanced with respect to stratification factors. The majority of patients had EGFR-positive tumours, 69% in the placebo and 70% in the erlotinib group. Most of the patients had stage IV NSCLC, 76% in placebo and 74% in the erlotinib group. The majority of patients received carboplatin plus gemcitabine or gemcitabine plus cisplatin as first line chemotherapy. The treatment groups were generally well balanced with respect to baseline tumour status. Similarly the treatment groups were generally well balanced with respect to tumour tissue sampling and biomarkers status. Approximately 70% of patients had tumours expressing the EGFR protein and <15% had EGFR-negative tumours.

Figure 1: Patient Disposition



[1] Patients were required to complete 4 cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or PD to be eligible for study randomization

Source: ex11_a

Results

Study BO18192 met its co-primary endpoints by demonstrating a statistically significant improvement in investigator assessed PFS ($p<0.0001$) for all patients (Hazard Ratio [HR]: 0.71, 95% confidence intervals [CI] 0.62-0.82) as well as for patients with EGFR-positive tumours (HR: 0.69, 95% CI 0.58-0.82) (Table 1). This corresponded to PFS improvements of 41% and 45% in all patients and in patients with EGFR-positive tumours respectively. The six month estimate of PFS rate was 25% in the erlotinib group compared with 15% in the placebo group.

Table 1: Summary of Progression Free Survival

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients included in analysis	447 (100.0 %)		437 (100.0 %)
Patients with event	400 (89.5 %)		349 (79.9 %)
Patients without event*	47 (10.5 %)		88 (20.1 %)
Time to event (weeks)			
Median#	11.1		12.3
95% CI for Median#	[8.1;11.7]		[12.0;13.3]
25% and 75%-ile	6.1;18.1		6.1;25.0
Range##	0.1 to 88.1		0.1 to 84.3
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.71	
95% CI		[0.62;0.82]	
6 months estimate			
Patients remaining at risk	53		83
Event Free Rate#	0.15		0.25
95% CI for Rate#	[0.12;0.19]		[0.21;0.29]

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: 17MAY2008

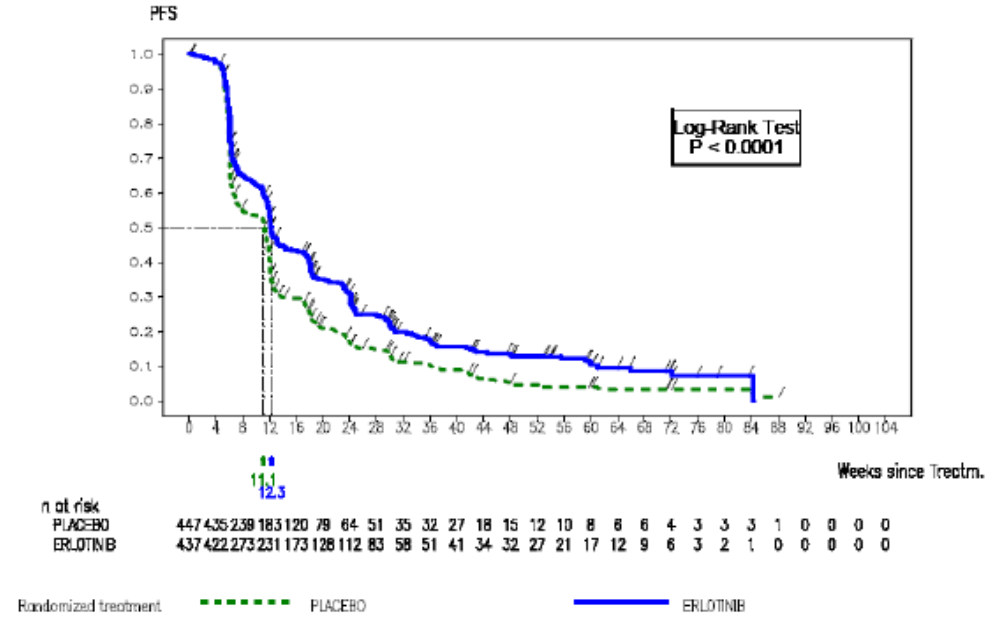
The robustness of the PFS assessment by the investigators was corroborated by the results of the independent central review of radiological and clinical data. PFS results from central review showed an HR of 0.71 (95% CI 0.61-0.84) in all patients and an HR of 0.66 (95% CI 0.54-0.80) in patients with EGFR-positive tumours. The robustness of the study results were also confirmed by stratified analysis, subgroup analysis and sensitivity analysis using various methods of censoring. The robustness of the PFS endpoint was also supported by secondary efficacy parameters.

Subgroup analyses showed consistent PFS benefit across subgroups, including patients with EGFR-negative tumours (HR: 0.77), patients with squamous histology (HR: 0.76) and patients with adenocarcinoma (HR: 0.60).

The HR for the primary parameter PFS according to investigator assessment based on the entire patient population was 0.71. The median PFS was 11.1 weeks in the placebo group versus 12.3 weeks in the erlotinib group. The six month estimate of PFS was 25% in the erlotinib group compared with 15% in the placebo group.

The Kaplan-Meier curves of PFS showed a clear separation (Figure 2) and both curves exhibited a step-wise decline corresponding with scheduled time points referencing assessment. The mean PFS was 16 weeks in the placebo group and 22.4 weeks in the erlotinib group being a difference of 6.4 weeks (36.6%).

Figure 2: Kaplan-Meier Curve of PFS



The HR for the co-primary endpoint PFS according to investigator assessment, based on the subgroup of patients with EFGR positive tumours is 0.69 (95% CI 0.58-0.82) is summarised in Table 2.

Table 2: Summary of PFS (Patients with EGFR IHC-positive tumours)

	PLACEBO (N=313)		ERLOTINIB (N=308)
Patients included in analysis	311 (100.0 %)		307 (100.0 %)
Patients with event	278 (89.4 %)		244 (79.5 %)
Patients without event*	33 (10.6 %)		63 (20.5 %)
Time to event (weeks)			
Median#	11.1		12.3
95% CI for Median#	[7.1;11.7]		[12.0;17.7]
25% and 75%-ile	6.0;18.1		6.1;29.9
Range##	0.1 to 88.1		0.1 to 78.9
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.69	
95% CI		[0.58;0.82]	
6 months estimate			
Patients remaining at risk	40		66
Event Free Rate#	0.16		0.27
95% CI for Rate#	[0.12;0.21]		[0.22;0.32]

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: 17MAY2008

[PDRD]Note: Patients with PD prior to randomization were excluded from PFS and TTP analysis. Therefore, the number of patients included in the analysis does not match the total number of patients included in the FAS

This demonstrated a highly significant benefit for the erlotinib group (p=<0.0001). The HR of 0.69 corresponds to a 45% improvement in PFS time in erlotinib-treated patients. The median PFS was 11.1 weeks for the placebo group versus 12.3 weeks in the erlotinib group. The mean PFS was 22.8 weeks in the erlotinib group and 16.2 weeks in the placebo group, being an increase of six weeks with 37% in the erlotinib group. The six months estimates of PFS rate was 27% in the erlotinib group compared with 16% in the placebo group. The Kaplan-Meier curves of PFS for the EFGR-positive subgroup were similar when compared to the overall population with a clear separation of the curves.

Review of OS data indicated that these data were immature (cut-off date 17 May 2008) when 403 patients or approximately 45% of randomised patients had died. A preliminary analysis of OS data is provided in Table 3. The HR was 0.92 (95% CI 0.762 -1.12, p=0.4107). This ratio plus the 95% CI were unaffected by whether the analysis was performed with or without inclusion of the stratification factors.

Table 3: Overall Survival

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients with event	209 (46.3 %)		194 (44.3 %)
Patients without event*	242 (53.7 %)		244 (55.7 %)
Time to event (months)			
Median#	11.3		11.5
95% CI for Median#	[10.2;13.0]		[10.3;13.7]
25% and 75%-ile	6.1;22.1		6.4;.
Range##	0.0 to 22.2		0.0 to 22.6
p-Value (Log-Rank Test)		0.4107	
Hazard Ratio		0.92	
95% CI		[0.76;1.12]	
1 year estimate			
Patients remaining at risk	98		101
Event Free Rate#	0.47		0.48
95% CI for Rate#	[0.41;0.52]		[0.42;0.54]

Survival [months] (TTDIED_M) - Censoring: Death Censoring (1=death, 0=censored) (CSDIED)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2008

A preliminary analysis of OS data conducted in the EGFR-positive subgroup showed similar results to the overall population as indicated in Table 4 with an HR of 0.89 (95% CI 0.7-1.14, p= 0.3638).

Table 4: OS (Patients with EGFR IHC-positive Tumours)

	PLACEBO (N=313)		ERLOTINIB (N=308)
Patients with event	136 (43.5 %)		130 (42.2 %)
Patients without event*	177 (56.5 %)		178 (57.8 %)
Time to event (months)			
Median#	12.1		12.7
95% CI for Median#	[9.7;15.2]		[10.9;15.1]
25% and 75%-ile	6.5;22.1		6.6;.
Range##	0.0 to 22.2		0.0 to 22.6
p-Value (Log-Rank Test)		0.3638	
Hazard Ratio		0.89	
95% CI		[0.70;1.14]	
1 year estimate			
Patients remaining at risk	67		75
Event Free Rate#	0.50		0.51
95% CI for Rate#	[0.43;0.57]		[0.45;0.58]

Survival [months] (TTDIED_M) - Censoring: Death Censoring (1=death, 0=censored) (CSDIED)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2008

In patients with EGFR-negative tumours there was a better PFS for the erlotinib group with an HR of 0.77. This was not statistically significant. The corresponding Kaplan-Meier curves of PFS showed a clear separation after Week 12 but this was not statistically significant (p=0.1768). The preliminary analysis of OS data in this EGFR-negative subgroup showed a HR of 0.83.

In relation to the response rates, the proportion of responses having a CR or PR after randomisation is more than twice as high in the erlotinib group compared with the placebo group (11.9% vs 5.4%, 95% CI 9.2-15.3% and 3.5-7.9%, p=0.0006). This is illustrated in Table 5. It was noted that the number of CRs was essentially the same in both groups but it was the number of PRs that were clearly higher in the erlotinib group of patients. The rate of stable disease was similar for the two groups. Independent review of these response rates corroborated the investigators' assessment of best response.

Table 5: Summary of Best Overall Response as Assessed by the Investigators

	PLACEBO (N=445)		ERLOTINIB (N=436)
Responders$	24 (5.4 %)		52 (11.9 %)
Non-Responders	421 (94.6 %)		384 (88.1 %)
95% CI for Response Rates*	[3.5; 7.9]		[9.0; 15.3]
Difference in Response Rates		6.53	
95% CI for Difference in Response Rates#		[2.7; 10.3]	
p-Value (Chi-squared Test)		0.0006	
Complete Response (CR)	3 (0.7 %)		4 (0.9 %)
95% CI for CR Rates*	[0.1; 2.0]		[0.3; 2.3]
Partial Response (PR)	21 (4.7 %)		48 (11.0 %)
95% CI for PR Rates*	[2.9; 7.1]		[8.2; 14.3]
Stable Disease (SD)	202 (45.4 %)		212 (48.6 %)
95% CI for SD Rates*	[40.7; 50.1]		[43.8; 53.4]
Progressive Disease (PD)	212 (47.6 %)		155 (35.6 %)
95% CI for PD Rates*	[42.9; 52.4]		[31.1; 40.2]
Missing (No Response Assessment)	7 (1.6 %)		17 (3.9 %)

Overall Best 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: 17MAY2008

Review of response upgrade after chemotherapy while on the randomised phase of treatment revealed that the rate of response upgrade was higher in the erlotinib group being 5.5% versus 1.3% (95% CI 3.6% - 8.1% vs 0.5% - 2.9%) and is indicated in Table 6. This difference was statistically significant (p=0.0007). The proportion of patients who had stable disease at baseline and had a response upgrade to PR during the study drug treatment period was 4.8% vs 0.9%. Only two patients in each treatment group had a response upgrade from PR to CR and one patient in the erlotinib group had a response upgrade from stable disease to CR.

Table 6: Summary of Response Upgrade Compared with Baseline – Investigator Assessment

	PLACEBO N=445		ERLOTINIB N=436
Patients with a Response Upgrade$	6 (1.3 %)		24 (5.5 %)
Patients with no Response Upgrade	439 (98.7 %)		412 (94.5 %)
95% CI for Response Upgrade Rates*	[0.5; 2.9]		[3.6; 8.1]
Difference in Response Upgrade Rates		4.2	
95% CI for Difference in Response Upgrade Rates#		[1.6; 6.7]	
p-Value (Chi-squared Test)		0.0007	
Patients with a Response Upgrade			
from PR to CR	2 (0.4 %)		2 (0.5 %)
95% CI for Rates*	[0.1; 1.6]		[0.1; 1.6]
from SD to PR	4 (0.9 %)		21 (4.8 %)
95% CI for Rates*	[0.2; 2.3]		[3.0; 7.3]
from SD to CR	0 (0.0 %)		1 (0.2 %)
95% CI for Rates*	[0.0; 0.8]		[0.0; 1.3]
Patients with no Response Upgrade			
from CR to CR	1 (0.2 %)		1 (0.2 %)
95% CI for Rates*	[0.0; 1.2]		[0.0; 1.3]
from PR to PR	17 (3.8 %)		27 (6.2 %)
95% CI for Rates*	[2.2; 6.0]		[4.1; 8.9]
from SD to SD	116 (26.1 %)		138 (31.7 %)
95% CI for Rates*	[22.0; 30.4]		[27.3; 36.2]
from CR to PD	0 (0.0 %)		0 (0.0 %)
95% CI for Rates*	[0.0; 0.8]		[0.0; 0.8]
from PR to SD	86 (19.3 %)		74 (17.0 %)
95% CI for Rates*	[15.8; 23.3]		[13.6; 20.8]
from PR to PD	103 (23.1 %)		72 (16.5 %)
95% CI for Rates*	[19.3; 27.3]		[13.2; 20.3]
from SD to PD	109 (24.5 %)		83 (19.0 %)
95% CI for Rates*	[20.6; 28.8]		[15.5; 23.0]
Missing (No Response Assessment Post Baseline)	7 (1.6 %)		17 (3.9 %)

$ Patients with a response upgrade from baseline
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
Cut-off for statistical analysis: 17MAY2008

Program : $PROD/cd11677d/bo18192/erup_t.sas
Output : $PROD/cd11677d/i18192m/reports/erup_t_2009.out
17NOV2008 12:59 Page 1 of 1

Review of subsequent treatment for these patient groups revealed that following randomised study treatment a greater proportion of patients in the placebo groups (64%) received second line and further line treatment compared with the erlotinib group (55%). With respect to the types of treatment received the percentage of patients was high in the placebo group for all the major classes of treatment compared with the erlotinib group, with the imbalance being particularly apparent in the EGFR tyrosine kinase inhibitor class of drug. In total 16% of patients received these drugs after placebo compared with 5% in the erlotinib group.

Review of quality of life analyses revealed that the time to symptom progression was similar in both treatment groups (HR: 0.91, 95% CI 0.74-1.12, p=0.3787). The time to deterioration in quality of life trial outcomes, which were physical wellbeing, functional wellbeing and lung cancer sub-scale

scores, were similar for both treatment groups with an HR of 1.06, 95% CI 0.87-1.31, p=0.5385 and is indicated in Table 7.

Table 7: Summary of Time to Deterioration in Trial Outcome Index

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients included in analysis	392 (100.0 %)		389 (100.0 %)
Patients with event	169 (43.1 %)		198 (50.9 %)
Patients without event*	223 (56.9 %)		191 (49.1 %)
Time to event (weeks)			
Median#	18.9		18.1
95% CI for Median#	[13.6;24.1]		[12.3;19.0]
25% and 75%-ile	6.7;49.1		6.4;.
Range##	2.3 to 85.1		2.0 to 72.3
p-Value (Log-Rank Test)		0.5385	
Hazard Ratio		1.06	
95% CI		[0.87;1.31]	
6 months estimate			
Patients remaining at risk	39		55
Event Free Rate#	0.41		0.39
95% CI for Rate#	[0.34;0.48]		[0.33;0.45]

Time to Deterioration in TOI [Weeks] (TTTTD_W) - Censoring: TTD Censoring (1=event, 0=censored) (CSTTD)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2008

Review of subgroup analyses of the primary endpoint revealed a robust and consistent PFS benefit across all the various subgroups. All HRs were below one except for the subgroup of patients with histologies other than squamous cell carcinoma and adenocarcinoma. Patients benefited from treatment whether or not they had previous surgery or radiotherapy and irrespective of the response to chemotherapy. Subgroup analyses conducted in the EGFR-positive population revealed results which were similar to the overall population.

Review of the biomarker subgroups revealed that all biomarker subgroups derived benefit in PFS from treatment with erlotinib as demonstrated by an HR of <1.

Patients derived benefit in PFS regardless of the FISH status. The HR was 0.68 in the EGFR FISH-positive subgroup and 0.81 in the EGFR FISH-negative subgroup.

Patients derived benefit in PFS regardless of EGFR mutation status with HR being 0.09 in the EGFR mutated subgroup and 0.81 in the EGFR wild-type subgroup.

Both K-ras mutated and wild-type subgroups benefited from treatment with erlotinib (HR: 0.77 and 0.70 respectively). These data indicate that the K-ras mutations are negative prognostic factors for PFS.

Review of OS for these various subgroups was not undertaken in view of the immature nature of the data in relation to this endpoint.

Comment

The data from this quite large and robust study has clearly shown a benefit for erlotinib in the maintenance phase of treatment in relation to PFS. This applies not only to the total patient population treated but also to particular subgroups, particularly the EGFR-positive subgroup. The

degree of benefit is convincing that there is a clearly statistically significant outcome. This is also reflected by the significant benefit in terms of improved response rates related to the patients receiving erlotinib in the maintenance stage of therapy. The data nevertheless is a little immature in that there is inadequate follow up duration available to clearly assess a possible benefit in relation to OS. This represents a disappointing feature of the study in that the application has been made before adequate follow-up duration is available to properly assess this endpoint. Nevertheless in the context of the primary endpoint chosen being PFS with a clearly highly significant result, it is reasonable to indicate that it is more likely than not that erlotinib will prove to be consistently beneficial in the maintenance phase of treatment for patients with advanced stage NSCLC and therefore warrants approval for a registration.

Updated Data

In response to a request from the TGA for updated data, the sponsor submitted an addendum to the original study report. The addendum report was dated August 2009 and the cut-off date for inclusion of data was 17 May 2009 (that is, an additional 12 months of follow-up).

The report addendum contained information on the following issues:

- An updated analysis of PFS in patients with activating mutations of EGFR and those with wild-type EGFR;
- An updated analysis of OS.

Updated PFS by biomarker analysis results

It was a mandatory requirement for entry into the study that for each patient, there must have been provided a tumour tissue sample. Biomarker analyses were performed on these samples to identify predictive factors for benefit from erlotinib treatment. Due to the limited amount of tissue available, biomarker testing was prioritised as follows:

- Protein expression level of EGFR by immunohistochemistry (IHC);
- Gene copy number of EGFR by fluorescence in situ hybridisation (FISH);
- Mutation status of K-ras by DNA sequencing;
- Mutation status of EGFR by DNA sequencing.

The results of the analysis of PFS by these biomarkers were presented in the original clinical evaluation. A striking finding from these analyses was that there appeared to be a very large PFS benefit with erlotinib treatment in patients with activating mutations of EGFR (HR: 0.09; 95% CI: 0.03 – 0.25). There were only 40 patients in the study with documented activating mutations of EGFR, with 22 treated with placebo and 18 with erlotinib.

There were 328 subjects with wild-type EGFR. Of these, 163 were treated with placebo and 165 with erlotinib. The analysis suggested that erlotinib therapy was also associated with some benefit in this group (HR: 0.81; 95% CI: 0.64 – 1.02).

In the study addendum, an updated analysis of these two patient subgroups was provided. In the original analysis of EGFR mutation status there were 100 tissue samples which either gave indeterminate results or could not be processed due to insufficient numbers of tumour cells available for DNA sequencing. Following modification of the testing methodology, EGFR mutation status could be determined for a further 69 of these 100 tumour samples. A total of 9 were found to have activating mutations of EGFR and 60 were found to have wild-type EGFR.

The revised analysis of PFS survival in patients with activating mutations of EGFR, including the 9 extra subjects, is summarised in Table 8. The HR was 0.23 (95% CI: 0.12 – 0.45; p = < 0.0001). Median PFS was increased from 13.0 months with placebo to 46.1 months with erlotinib. Although

the hazard reduction was not as impressive as seen in the original analysis (HR = 0.10), the result still suggests that erlotinib is likely to be particularly effective in this subgroup.

Table 8: PFS in subjects with activating mutations of EGFR (data cut-off 17 May 2009).

	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)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2009

The revised analysis of PFS survival in patients with wild-type EGFR, including the 60 extra subjects, did not result in any notable change in result (HR: 0.78; 95% CI not given).

Updated Overall Survival results

In the original study report the data for OS were immature with only 403 of 889 patients (45 %) having died. The addendum report was based on an additional 12 months of follow-up, and by this stage 648 of 889 patients (73 %) had died.

OS (all patients)

The results for OS for all patients enrolled in the trial are summarised in Table 9. Compared to placebo, erlotinib maintenance treatment was associated with a modest but statistically significant improvement in OS (HR: 0.81, 95%CI: 0.70 to 0.95; p=0.0088). Median survival was increased from 11.0 to 12.0 months. An extra 5% of patients (50% vs 45%) were alive after 12 months.

Table 9: OS in all patients

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients with event	350 (77.6 %)		298 (68.0 %)
Patients without event*	101 (22.4 %)		140 (32.0 %)
Time to event (months)			
Median#	11.0		12.0
95% CI for Median#	[9.9;12.1]		[10.6;13.9]
25% and 75%-ile	6.0;20.2		6.4;24.4
Range##	0.0 to 33.4		0.0 to 34.1
p-Value (Log-Rank Test)		0.0088	
Hazard Ratio		0.81	
95% CI		[0.70;0.95]	
1 year estimate			
Patients remaining at risk	196		204
Event Free Rate#	0.45		0.50
95% CI for Rate#	[0.41;0.50]		[0.45;0.55]

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

Effect of subsequent treatments on OS (all patients)

Patients were continued on erlotinib or placebo until disease progression or unacceptable toxicity developed. They could then receive second and further lines of therapy in an uncontrolled fashion. Approximately 70% of subjects in each arm received such therapy. Second line tyrosine kinase inhibitor (TKI) treatment (for example erlotinib or gefitinib) was received by 21% of subjects the placebo arm, and 11% of subjects in the erlotinib arm, as shown in Table 10. Other types of second or later line treatments (various types of chemotherapy, radiotherapy, surgery) were equally distributed across the two treatment arms.

Table 10: Second or later line treatment with tyrosine kinase inhibitors

Class/ Other Treatment or Procedure	PLACEBO N = 451 No. (%)	ERLOTINIB N = 438 No. (%)
TYROSINE KINASE INHIBITORS		
Total Pts With at Least one Treatment	95 (21)	50 (11)
ERLOTINIB	67 (15)	33 (8)
GEFITINIB	27 (6)	9 (2)
BLINDED VANDETANIB	6 (1)	4 (<1)
VANDETANIB	2 (<1)	4 (<1)
BLINDED SUNITINIB	5 (1)	-
*ERLOTINIB/*PROTEIN TYROSINE KINASE INHIBITOR	1 (<1)	-
BLINDED (ERLOTINIB/VANDETANIB)	1 (<1)	-
BLINDED SUNITINIB/ERLOTINIB	1 (<1)	-
PF-00299804	1 (<1)	-
SORAFENIB	1 (<1)	-
SUNITINIB	1 (<1)	-
Total Number of Treatments	113	50

Percentages are based on N.
Multiple occurrences of the same treatment in one individual counted only once.
* Ingredient may not be in the treatment; it is not in all formulations in all countries.
Cut-off for statistical analysis: 17MAY2009

Due to the imbalance in second line TKI treatment, the sponsor conducted a post-hoc analysis of OS where patients were censored at the time of their first use of TKIs after completion of the randomised erlotinib/placebo part of the study. The results of this analysis are shown in Table 11. Compared to the all patients OS analysis, the HR was essentially unchanged (0.77 vs 0.80). The difference in median survival between erlotinib and placebo increased from 1.0 month (12.0 vs 11.0) to 1.9 months (12.5 vs 10.6).

Table 11: Post Hoc analysis – OS censored for second line tyrosine kinase inhibitor use.

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients with event	284 (63.0 %)		279 (63.7 %)
Patients without event*	167 (37.0 %)		159 (36.3 %)
Time to event (months)			
Median#	10.6		12.5
95% CI for Median#	[9.6;11.6]		[10.6;14.5]
25% and 75%-ile	5.8;19.7		6.5;24.1
Range##	0.0 to 33.4		0.0 to 34.1
p-Value (Log-Rank Test)		0.0087	
Hazard Ratio		0.80	
95% CI		[0.68;0.95]	
1 year estimate			
Patients remaining at risk	143		189
Event Free Rate#	0.44		0.51
95% CI for Rate#	[0.39;0.49]		[0.46;0.55]

* censored
\# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2009

OS for biomarker subgroups

The HRs for all biomarker subgroups were below 1.0, suggesting benefit for all subgroups. The survival benefit was statistically significant in the EGFR IHC-positive and EGFR wild-type mutation status subgroups.

Of note, the survival benefit had not reached statistical significance in the subgroup of patients with activating mutations of EGFR (Table 12), despite the impressive prolongation of PFS associated with erlotinib treatment in this subgroup, as described above. The sponsor's explanation for this observation was that the survival data in this subgroup were immature, with only 8 of 22 patients (36%) in the erlotinib arm, and 13 of 27 patients (48%) in the placebo arm having died. (In each of the other biomarker subgroups over 65% of subjects had died). The sponsor also noted that 18/27 (67%) of placebo-treated patients in the activating mutation subgroup had received tyrosine kinase inhibitors (mainly erlotinib or gefitinib) as second line treatment after progression. Given this high rate of crossover it is possible that any survival benefit produced by the drug in the EGFR activating mutation subgroup will have been obscured.

Table 12: OS in patients with activating mutations of EGFR

	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

OS for other subgroups

A reasonably consistent effect was seen across all these subgroups with HR values all being below 1.00.

Conclusion

The updated efficacy data indicate that use of erlotinib as maintenance therapy following first line chemotherapy results in a modest survival benefit.

Safety

The safety population in study BO18192 involved 878 patients (433 in the erlotinib group and 445 in the placebo group). Patients for whom both study drugs were inadvertently dispensed (three in each treatment group) were excluded from the exposure analyses.

Safety evaluations performed included documentation of adverse events and routine clinical laboratory tests. The treatment phase of the study began at the time of randomisation and continued to 28 days after last dose of study drug. Patients with serious adverse events considered by the investigator to be related to the study drug were followed until resolution of the event. A treatment emergent adverse event was defined as any untoward medical occurrence during the treatment phase whether or not it was considered related to the study drug administration. Pre-existing conditions that worsened during study were to be reported as adverse events and adverse events occurring within 28 days of the last dose of study drug were also considered to be treatment emergent. The intensity of adverse events was rated on a five point scale according to National Cancer Institute common toxicity criteria.

Exposure

Review of the extent of exposure of the safety population is summarised in Table 13.

Table 13: Summary of Extent of Exposure (Safety Population)

	PLACEBO N = 442 No. (%)	ERLOTINIB N = 430 No. (%)
TRIAL DRUG MG		
Treatment Duration (months)		
0 - 0.9	16 (4)	21 (5)
1 - 1.9	179 (40)	142 (33)
2 - 2.9	99 (22)	60 (14)
3 - 3.9	27 (6)	30 (7)
4 - 4.9	40 (9)	46 (11)
5 - 5.9	23 (5)	35 (8)
6 - 6.9	10 (2)	13 (3)
7 - 7.9	13 (3)	22 (5)
8 - 8.9	8 (2)	16 (4)
9 - 9.9	4 (<1)	7 (2)
10 - 999	23 (5)	37 (9)
Total Cumulative Dose (MG)		
Mean	15273.8	18509.4
SD	14029.16	16418.57
SEM	667.30	791.77
Median	12300.0	12750.0
Min	750	0
Max	88500	89400
n	442	430

Percentages are based on N.
Patients for whom inadvertently both study drugs were dispensed are excluded from this analysis.
Cut-off for statistical analysis: 17MAY2008

	PLACEBO N = 442	ERLOTINIB N = 430
Treatment Duration [weeks]		
Mean	14.70	18.59
SD	13.754	16.678
SEM	0.654	0.805
Median	11.71	12.29
Min-Max	0.9 - 92.7	0.6 - 85.1
n	442	429

n represents number of patients contributing to summary statistics.
Patients for whom inadvertently both study drugs were dispensed are excluded from this analysis.
Cut-off for statistical analysis: 17MAY2008

The median total cumulative dose of erlotinib was 12,750 mg with a median exposure of 12.3 weeks. The placebo group had a shorter median duration of exposure (11.7 weeks) which correlates with the shorter PFS in this group. Ninety-five patients (22%) received erlotinib for more than six months compared with 58 patients (13%) in the placebo group.

The majority of patients in the erlotinib group maintained the initial starting dose of 150 mg throughout study but 11% had their erlotinib dose reduced to 100 mg and four patients had a dose reduction to <100 mg per day.

Adverse Events

Review of the overall incidence of adverse events revealed in the erlotinib group, 78.8% experienced one or more adverse events, while for the placebo group this was 54.2%. A total of 20 patients (4.6%) stopped taking the study drug due to an adverse event compared to placebo (1.6%) and 16.2% of patients had a dose modification interruption due to an adverse event compared to 3.4% taking placebo (Table 13).

Table 13: Overview of Adverse Events, Withdrawals and Deaths

	PLACEBO N = 445 No. (%)	ERLOTINIB N = 433 No. (%)
Total Pts with at Least one AE	241 (54.2)	341 (78.8)
Total Number of AEs	700	1268
Deaths #	31 (7.0)	35 (8.1)
Study withdrawals due to an AE #	7 (1.6)	19 (4.4)
Patients with at least one		
AE leading to Death	5* (1.1)	10 (2.3)
Serious AE	34 (7.6)	47 (10.9)
Related serious AE	1 (0.2)	10 (2.3)
AE leading to withdrawal from treatment	7 (1.6)	20 (4.6)
AE leading to dose modification/interruption	15 (3.4)	70 (16.2)
Related AE	89 (20.0)	281 (64.9)
Related AE leading to withdrawal from treatment	2 (0.4)	12 (2.8)
Severe AE	54 (12.1)	107 (24.7)

Investigator text for Adverse Events encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.
Deaths occurred during treatment phase are counted.
Cut-off for statistical analysis: 17MAY2008
AE24 17NOV2008:14:48:14 (1 of 1)
* NOTE: An additional Grade 5 AE of pulmonary embolism was recorded on the survival CRF page. No SAE form was received for this AE. [PDRD]

Common Adverse Events

Review of common adverse events were consistent with the findings from other clinical studies with erlotinib, that is, rash (49.2%) and diarrhoea (20.3%) were the most commonly reported adverse events in the erlotinib group. These are the only adverse events with an incidence of >10%. Table 14 displays a listing of all adverse events with an incidence of at least 3% among the erlotinib-treated patients. Those adverse events on the erlotinib arm of treatment with an incidence clearly higher than those patients receiving placebo included several skin and subcutaneous tissue disorders, pruritus, acne, dermatitis acneiform, dry skin as well as diarrhoea, nausea, fatigue, asthenia, pneumonia, paronychia, anorexia and weight decrease.

Table 14: Adverse Events Reported in ≥3% of Patients in the Erlotinib Group

Body System/ Adverse Event	Placebo N=445						Erlotinib N=433					
	All		G3		G4		All		G3		G4	
	N	%	N	%	N	%	N	%	N	%	N	%
Skin and Subcutaneous Tissue Disorders												
Rash	26	5.8	-	-	-	-	213	49.2	26	6.0	-	-
Pruritus	12	2.7	-	-	-	-	32	7.4	1	<1	-	-
Acne	-		-	-	-	-	27	6.2	3	<1	-	-
Dermatitis Acneiform	5	1.1	-	-	-	-	20	4.6	4	<1	-	-
Dry Skin	4	0.9	-	-	-	-	19	4.4	-	-	-	-
Gastrointestinal Disorders												
Diarrhoea	20	4.5	-	-	-	-	88	20.3	8	1.8	-	-
Nausea	27	6.1	-	-	-	-	33	7.6	-	-	-	-
Vomiting	14	3.1	-	-	-	-	15	3.5	-	-	-	-
Respiratory, Thoracic and Mediastinal Disorders												
Cough	38	8.5	4	<1	-	-	36	8.3	-		-	-
Dyspnoea	39	8.8	6	1.3	-	-	34	7.9	6	1.4	1	<1
Haemoptysis	23	5.2	1	<1	1	<1	23	5.3	1	<1	-	-
General Disoreders and Administration Site Conditions												
Fatigue	26	5.8	5	1.1	-	-	39	9.0	8	1.8	-	-
Chest Pain	28	6.3	6	1.3	-	-	15	3.5	1	<1	-	-
Asthenia	13	2.9	4	<1	-	-	18	4.2	3	<1	-	-
Metabolism and Nutrition Disorders												
Anorexia	22	4.9	1	<1	-	-	40	9.2	2	<1	-	-
Infections and Infestations												
Pneumonia	7	1.6	4	<1	-	-	13	3.0	7	1.6	-	-
Paronychia	-		-	-	-	-	17	3.9	3	<1	-	-
Nervous System Disorders												
Headache	13	2.9	2	<1	-	-	14	3.2	1	<1	-	-
Investigations												
Weight Decreased	4	0.9	-	-	-	-	17	3.9	1	<1	-	-

Severe Adverse Events

Throughout the study most adverse events were generally Grade I or II in severity with 54% of patients receiving erlotinib being in this category and 42% of patients receiving placebo. There were a higher proportion of patients in the erlotinib group who experienced at least Grade III adverse events, 24% vs 12.1% for placebo. Body systems most commonly associated with this level of severity among patients receiving erlotinib were *Skin and Subcutaneous Disorders* (9% vs 0%), *Gastrointestinal Disorders* (3.9% vs 1.0%) and *Infections* (3.7% vs 1.6%). Review of deaths in the study revealed that 35 patients (8.1%) in the erlotinib group and 31 patients (7%) in the placebo group died during the treatment phase. They were assessed by the investigators at the time of the study completion; nine patients in the erlotinib group and three patients in the placebo group died during the treatment phase due to an adverse event. None of these events have been assessed as causes related to erlotinib by investigators. It is noteworthy that one of the patients who was assessed as dying from progressive disease also had evidence of interstitial lung disease (ILD)while on treatment which had been progressive and therefore maybe considered to be potentially drug related.

Serious Adverse Events

Review of serious adverse events revealed that 10.9% of patients in the erlotinib group experienced one or more serious adverse events compared with 7.6% of patients receiving placebo. Ten patients in the erlotinib group and one in the placebo group experienced serious adverse events that were regarded by investigators as related to the trial treatment. These included three patients with diarrhoea, two patients with rash, two patients with ILD and one patient with pulmonary fibrosis. One patient also had elevation of liver enzymes and another a respiratory tract infection, all possibly related to erlotinib treatment.

Withdrawals

Review of adverse events leading to withdrawal from treatment revealed that 20 patients (4.6%) in the erlotinib group and seven patients (1.6%) in the placebo group discontinued study medication as a result of an adverse event. Among the erlotinib patients 12 of these were considered related to study drug. Five had treatment withdrawn due to rash, two due to diarrhoea. Other adverse events leading to withdrawal of erlotinib included ILD, two cardio-respiratory arrests, dermatitis acneiform, gastric perforation, pneumonia, non-cardiac chest pain, pulmonary fibrosis, fatigue, urogenital haemorrhage, cardiac failure, dyspnoea and transaminase increased. In the erlotinib group 36 patients (8.3%) had dose modifications due to rash and 14 patients (3.2%) had dose modifications due to diarrhoea.

Adverse Events of Special Interest

Review of adverse events of special interest confirmed the relatively high incidence of rash as a significant adverse event associated with erlotinib administration (Table 15). Thirty six patients had dose modifications due to rash and five patients had treatment withdrawn due to rash. Two of the patients experienced serious rash. Two thirds of these patients experienced a rash within the first two weeks of treatment.

The other adverse event of particular interest was that of ILD. Three patients (0.7%) in the erlotinib group experienced ILD-like events compared with none in the placebo group (Table 15). All three of these events were serious and one case possibly led to the death of the patient. A second case of ILD resolved with sequelae and the third patient had pulmonary fibrosis which persisted until their death from progressive disease. No lung biopsies were performed on these patients and therefore histological confirmation was not available.

Table 15: Summary of Rash and ILD by Predefined Preferred Terms

Medical Concept/ Adverse Event	PLACEBO N = 445 No. (%)	ERLOTINIB N = 433 No. (%)
RASH		
Total Pts With at Least one AE	42 (9.4)	261 (60.3)
RASH	26 (5.8)	213 (49.2)
ACNE	-	27 (6.2)
DERMATITIS ACNEIFORM	5 (1.1)	20 (4.6)
SKIN FISSURES	-	6 (1.4)
ERYTHEMA	3 (0.7)	2 (0.5)
RASH PAPULAR	1 (0.2)	3 (0.7)
RASH GENERALISED	-	3 (0.7)
RASH PRURITIC	3 (0.7)	-
SKIN EXFOLIATION	-	3 (0.7)
URTICARIA	2 (0.4)	1 (0.2)
DERMATITIS	-	2 (0.5)
ECZEMA	1 (0.2)	1 (0.2)
EXFOLIATIVE RASH	-	2 (0.5)
DERMATITIS EXFOLIATIVE	-	1 (0.2)
FURUNCLE	-	1 (0.2)
RASH MACULAR	1 (0.2)	-
RASH PUSTULAR	-	1 (0.2)
SKIN HYPERPIGMENTATION	-	1 (0.2)
SKIN REACTION	-	1 (0.2)
SKIN ULCER	-	1 (0.2)
Total Number of AEs	42	289
INTERSTITIAL LUNG DISEASE (WIDE)		
Total Pts With at Least one AE	-	3 (0.7)
INTERSTITIAL LUNG DISEASE	-	2 (0.5)
PULMONARY FIBROSIS	-	1 (0.2)
Total Number of AEs	-	3

Adverse event investigator text encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 17MAY2008

A summary of adverse events according to System Organ Class (SOC) is shown in Table 16. As previously indicated *Skin and Subcutaneous Tissue Disorders* and *Gastrointestinal Disorders* were particularly prominent in the erlotinib treated patients. These differences were particularly related to the high incidence of rash and diarrhoea in the erlotinib patients as discussed above.

Table 16: Summary of Adverse Events by Body System

Body System/ Adverse Event	PLACEBO N = 445 No. (%)	ERLOTINIB N = 433 No. (%)
ALL BODY SYSTEMS	241 (54.2)	341 (78.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	56 (12.6)	273 (63.0)
GASTROINTESTINAL DISORDERS	71 (16.0)	132 (30.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	92 (20.7)	93 (21.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	71 (16.0)	103 (23.8)
INFECTIONS AND INFESTATIONS	36 (8.1)	73 (16.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	53 (11.9)	43 (9.9)
NERVOUS SYSTEM DISORDERS	47 (10.6)	48 (11.1)
METABOLISM AND NUTRITION DISORDERS	31 (7.0)	45 (10.4)
INVESTIGATIONS	11 (2.5)	31 (7.2)
EYE DISORDERS	10 (2.2)	21 (4.8)
VASCULAR DISORDERS	19 (4.3)	12 (2.8)
PSYCHIATRIC DISORDERS	9 (2.0)	20 (4.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11 (2.5)	12 (2.8)
CARDIAC DISORDERS	9 (2.0)	12 (2.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	10 (2.2)	10 (2.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (1.1)	6 (1.4)
EAR AND LABYRINTH DISORDERS	1 (0.2)	7 (1.6)
RENAL AND URINARY DISORDERS	3 (0.7)	4 (0.9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (0.4)	4 (0.9)
HEPATOBILIARY DISORDERS	2 (0.4)	3 (0.7)

Investigator text for Adverse Events encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 17MAY2008

In the SOC of *General Disorders and Administration Site Conditions*, there was a higher incidence of adverse events in the erlotinib group than the placebo group but these were generally mild to moderate in nature. Adverse events included fatigue (9% vs 5.8%), asthenia (4.2% vs 2.9%), pyrexia (2.8% vs 1.1%) and mucosal inflammation (1.6% vs 0.2%).

The incidence of *Infections and Infestations* was 16.9% in the erlotinib group compared with 8% in the placebo group primarily due to 17 patients in the erlotinib group experiencing paronychia while no cases of paronychia occurred in the placebo group. There were 13 patients (3.3%) in the erlotinib group who experienced pneumonia compared to seven in the placebo group and a further seven patients in the erlotinib group had respiratory tract infections compared to two in the placebo group.

There was a higher incidence of anorexia among patients receiving erlotinib (9.2% vs 4.9%).

There was a higher incidence of *Eye Disorders* in the erlotinib compared to placebo which primarily reflected the higher incidence of conjunctivitis (9 patients vs 3 patients).

Laboratory Values

There was a higher incidence in the erlotinib group compared with the placebo group of weight decrease (3.9% vs 0.9%), aspartate aminotransferase (AST) increased (7 vs 2 patients), alanine aminotransferase (ALT) increased (6 vs 2 patients), bilirubin increased (4 vs none) and transaminases increased (3 patients vs none). This raised the question of a small potential for hepatic function disorders associated with erlotinib administration.

Minor changes in haematological parameters occurred in both treatment groups with the emphasis being a little higher in terms of decreased white blood count for patients receiving erlotinib, with Grade I abnormalities of this type being experienced by 15 patients receiving erlotinib versus nine receiving placebo. Electrocardiogram (ECG) changes were minor and similar for both treatment groups. Similarly there were no significant differences in vital signs changes for both treatment groups. Review of intrinsic factors including gender, age, race and performance status revealed that the data was similar to that from previous erlotinib studies in that in general adverse event incidences were higher among women compared with men, older patients compared with younger patients and ECOG 1 performance status compared with ECOG 0 patients. Also consistent with previous analyses was the observation that Asians have a noticeably higher incidence of adverse events when compared with Caucasians.

Comment

These data have essentially shown that the adverse event profile for erlotinib in the SATURN study is similar to that previously observed from other clinical trials involving erlotinib administration. The increased incidence of rash and diarrhoea in particular are well described. There is now a little more evidence that ILD may be related to erlotinib administration, and although a relatively uncommon adverse event, it is one that requires appropriate monitoring. This study has brought to light the possibility of potential for hepatic function disturbance in relation to erlotinib administration and this will also require appropriate monitoring. In general terms, the adverse event profile for erlotinib administration may be considered manageable and in line with previous experience. There is no impediment to consideration of approval for erlotinib for maintenance therapy in the context of concern regarding the safety profile.

Post-Marketing Experience

Erlotinib was first approved on 18 November 2004. As of 17 November 2008 erlotinib has been approved in more than 90 countries. During this four year period an estimated 313,000 patients were treated with erlotinib in the post-marketing setting and in clinical trials. A total of seven Periodic Safety Update Reports (PSURs) have been provided and during this period a total of 11,118 adverse events of which 6,381 were serious were received in 5,010 patients across several indications. A total of 990 deaths have been reported. A large proportion of these were secondary to disease progression. Most frequently reported adverse events in cancer patients treated with erlotinib included diarrhoea, vomiting, nausea and intestinal perforation. Also included among *Skin and Subcutaneous Tissue Disorders* were rash, dermatitis acneiform and among *General Disorders*, were fatigue and pyrexia. In terms of cardio-respiratory disorders, ILD, dyspnoea and pulmonary embolism were reported.

Among new warnings and precautions provided as a result of these updates include gastrointestinal perforation and its potential risk with erlotinib; the potential concern regarding an incidence of ILD; a potential concern regarding an incidence of drug-induced liver injury; ongoing warnings related to incidence of diarrhoea and of sequelae; and the potential for serious skin conditions and ocular toxicities including possible corneal perforation.

Clinical Summary and Conclusions

The data provided in this submission are essentially those associated with a full report related to the study BO18192, SATURN. This is a multicentre, double-blind, randomised Phase III study to evaluate the efficacy of Tarceva or placebo following four cycles of platinum-based chemotherapy in patients with histologically documented advanced or recurrent stage IIIB or stage IV NSCLC who have not experienced disease progression or unacceptable toxicity during chemotherapy. This study was initiated on 29 March 2006 and the cut-off date for evaluation for this report was the 17 May 2008.

The primary objectives of the trial were to determine if administration of erlotinib after standard platinum-based chemotherapy for the treatment of NSCLC results in improved PFS when compared with placebo in the overall population, and to determine if administration of erlotinib after standard platinum-based chemotherapy in the treatment of NSCLC results in improved PFS when compared with placebo in patients who have EGFR receptor protein expression-positive tumours.

Review of the clinical pharmacology data from this trial which included assessment of 308 patients who had available PK/PD data. The data provide from these analyses were in line with those previously reported in patients receiving erlotinib for stage IIIB/IV NSCLC. Consistent with this was that apparent clearance was slightly higher in current smokers by approximately 20% compared to those who had never smoked. There was no obvious relationship between measures of exposure in either efficacy or safety parameters identified.

Review of the outcomes of the co-primary endpoints demonstrated as statistically significant improvement in investigator assessed PFS with a p value of <0.0001 for all patients (HR 0.71, 95% CI 0.62-0.82). This is also apparent for patients with EGFR-positive tumours with an HR of 0.69, (95% CI 0.58-0.82). This corresponded to a PFS improvement of 41% and 45% in all patients and the EGFR-positive population respectively. The six month estimate of PFS rate for all patients was 25% in the erlotinib group compared with 15% in the placebo group. Mean PFS was 22.4 weeks in the erlotinib group compared with 16 weeks in the placebo group for the overall population. Similar results were observed in the EGFR-positive population.

The results were found to be robust with corroboration of the data from an independent central review of radiological and clinical outcomes. Stratified analysis and subgroup analysis also confirmed this. Subgroup analyses showed consistent PFS benefit across subgroups including patients with EGFR-negative tumours with an HR 0.77, patients with squamous histology with an HR of 0.76 while patients with adenocarcinoma had an HR of 0.6. Benefit was also observed across all biomarker subgroups.

Patients in the erlotinib arm achieved a significantly higher response rate compared to the placebo arm, 11.9% vs 5.4%, p=0.0006 and response upgrade rate of 5.5% vs 1.3%, p=0.0007.

Review of data regarding OS however failed to reveal any significant differences between two arms of study, although it is recognised that the duration of follow-up is somewhat short and the planned number of deaths before full evaluation of OS have not yet been reached. Similarly there were no significant differences in OS between any of the treatment subgroups.

With regards to quality of life there was no evidence of any differences between the two treatment arms in relation to time to symptom progression or time to deterioration in trial outcomes.

In relation to safety more patients in the erlotinib group than the placebo group experienced at least one adverse event, 78.8% compared to 54.2%. More patients withdrew from the study due to an adverse event related to erlotinib, 4.6% compared to 1.6%. The majority of adverse events reported were of mild or moderate intensity. The number of patients who experienced a severe adverse event was 24.7% in the erlotinib group versus 12.1% in the placebo group. The incidence of adverse events considered to be related to study treatment by investigator was higher in the erlotinib group than the placebo group, 64.9% versus 20%. A large proportion of differences were due to larger incidence of patients who developed rash or diarrhoea in the erlotinib group.

Sixty six patients died during the treatment phase, 35 were receiving erlotinib and 31 placebo. Nine patients in the erlotinib group and four in the placebo group died during the treatment phase due to an adverse event. None of these events had been assessed as causally related to erlotinib. Only one death maybe possibly related to erlotinib, namely a patient who died with ILD. The investigators' final assessment of this was progressive malignancy.

There was a higher incidence of serious adverse events among the erlotinib treated patients, 10.9% versus 7.6%. This again principally related to *Skin and Subcutaneous Tissue Disorders* as well as *Gastrointestinal Disorders* reflecting the incidences of rash and diarrhoea. Adverse effects of importance, which appear to require ongoing monitoring in relation to erlotinib, include ILD, hepatic function disorders and eye disorders. Laboratory safety evaluation did not reveal any major differences except for a minor increase in the incidence of hepatic enzyme disturbances in line with concern regarding potential disturbance of hepatic function related to erlotinib administration.

The data from study BO18192, SATURN have therefore demonstrated a clear-cut improvement in PFS for those patients receiving maintenance therapy with erlotinib after earlier chemotherapy. This is a clear-cut statistical level benefit. The study is quite large and robust. Subgroup analyses confirm the positive data in relation to the PFS primary endpoint. This is further emphasised via a positive outcome in relation to PFS for patients with EGFR-positive tumours. It is disappointing that the data are not mature enough to be able to assess any potential OS differences. Certainly it would be important to maintain follow-up throughout the duration of this study to confirm any possible benefits in the longer term.

The toxicity profile for erlotinib in this study is commensurate with that previously seen from earlier studies of erlotinib and in line with that generally anticipated for this agent. No new concerns have been raised as a result of this study, although emphasis on the need for monitoring in relation to interstitial lung disease and hepatic function disturbances is apparent.

The evaluator considered that the data provided in this submission in regards to potential benefit for erlotinib, for the proposed indication for maintenance therapy in patients with locally advanced or metastatic NSCLC who have not progressed on first line chemotherapy, have been met and therefore supported approval of this proposed indication.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendation.

Quality

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

Non-Clinical

There was no requirement for a non-clinical assessment in an application of this type.

Clinical

The clinical evaluator recommended approval of the application.

Evidence to support the new indication comes from a single randomised, double-blind, placebo controlled trial (study BO18192 or SATURN). The study has only been published in conference abstract format. There are two clinical evaluation reports. Following completion of the initial clinical evaluation, the sponsor provided some updated efficacy data.

The trial enrolled subjects with locally advanced or metastatic NSCLC. All subjects received first line chemotherapy with 4 cycles of a platinum-based doublet. Those without disease progression (n = 889) were then randomised to receive either erlotinib (n = 438) or placebo (n = 451). Treatment was continued until disease progression, death or the development of unacceptable toxicity.

Pharmacokinetics

The study generated some population pharmacokinetic data. The pharmacokinetics of erlotinib in the trial were consistent with previously evaluated data. A PK/PD analysis could not establish any relationship between erlotinib AUC and adverse effects or efficacy parameters.

Efficacy

There were two co-primary endpoints for the study:

- Progression free survival (PFS) in the overall population; and
- PFS in the population of patients whose tumours over-expressed EGFR.

Erlotinib treatment was associated with a significant reduction in the risk of progression or death (HR: 0.71; 95% CI: 0.62 to 0.82; $p < 0.0001$). PFS at 6 months was increased by 10% (25% vs 15%). Median PFS was only slightly prolonged (12.3 vs 11.1 weeks). However, median PFS in this study underestimates the efficacy benefit, as the Kaplan-Meier curves converged at the median. Results for the EGFR-positive population were similar.

Overall survival (OS) was a secondary endpoint for the study. Erlotinib was associated with a statistically significant but clinically modest efficacy benefit (HR: 0.81; 95% CI: 0.70 – 0.95; $p = 0.0088$). Median survival was increased from 11.0 to 12.0 months. The proportion of patients alive after 12 months was increased by 5% (50% vs 45%).

Subgroup analyses suggested benefit on the PFS endpoint in most subgroups. The drug appeared to be notably effective in patients with activating mutations of the EGFR gene (HR: 0.09; 95% CI: 0.03 to 0.25).

Erlotinib was associated with a significant increase in response rate (11.9% vs 5.4%). There were no significant differences between treatment groups with respect to quality of life measures.

Safety

The safety profile of erlotinib in the submitted study was consistent with that observed in previously evaluated studies. Erlotinib treatment was associated with increased incidences of dermatological and gastrointestinal adverse events and fatigue and asthenia. The majority of adverse effects were of Grade I or II in severity. The overall incidence of Grade III or IV adverse events was also increased (24% vs 12%).

The toxicity associated with erlotinib appeared manageable, as the incidence of patients withdrawing from treatment due to adverse events was only slightly elevated (4.6% vs 1.6%).

In the erlotinib arm, there was an increased incidence of deaths not due to disease progression (9 vs 4). One patient had interstitial lung disease (ILD), a known adverse effect of the drug. The other deaths were not considered related to erlotinib.

Risk-Benefit Analysis

Delegate Consideration

The submitted study demonstrated a statistically significant benefit for erlotinib over placebo with respect to PFS and OS. The magnitude of the effect was modest, as only an extra 10% of subjects were alive and free of disease progression at 6 months, and only an extra 5% of subjects were alive at 12 months. Toxicity was consistent with that observed in previously evaluated studies.

Erlotinib is currently approved for use in NSCLC patients who have experienced disease progression following first line chemotherapy. This approval was based on a Phase III trial which demonstrated significantly improved OS compared to placebo (median survival 6.7 vs 4.7 months).

The current application seeks approval for the incorporation of erlotinib into first line therapy. This approach has also been shown to produce a survival benefit compared to placebo (median survival 12.0 vs 11.0 months). It is possible that patients may have a better overall outcome if erlotinib therapy is delayed until disease progression occurs, rather than commencing the drug immediately on completion of first line chemotherapy. This question could be answered with a randomised study comparing early versus late use of erlotinib, but such data are not available.

According to the authors of one of the conference abstracts describing the study, a substantial proportion of patients do not receive second line therapy, possibly because of worsening overall condition. If this is correct, it would be an argument in favour of the use of erlotinib as part of first line therapy.

The maintenance therapy strategy has been shown to produce a survival benefit and the toxicity of erlotinib was manageable. The Delegate therefore believed that the risk-benefit profile of maintenance therapy strategy is favourable and proposed to approve the application. The product information should contain a statement that there are no data available to assess which of the two treatment strategies is superior.

Advisory Committee Consideration

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal.

ADEC recommended rejection of the application on the grounds that although the study showed statistical significance, this did not translate into meaningful clinical efficacy. Moreover, there were no significant differences between treatment groups with respect to quality of life measures. In addition, the study indicated that there was an increase in overall incidence of Grade III and IV adverse events (24% vs 12%), thus did not yield a positive risk benefit ratio.

Initial Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Tarceva, containing erlotinib 25 mg, 100 mg and 150 mg 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

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutics Goods Act whereby a review of the initial decision is conducted by the Minister.

The Delegate of the Minister noted that the Delegate's reasons in support of his rejection were:

-that the efficacy benefits of erlotinib maintenance therapy in patients with NSCLC are modest and are outweighed by the toxicity produced by the drug;

-an alternative therapy (pemetrexed) exists for patients with NSCLC with non-squamous histology, which has a favourable risk-benefit ratio, and which, on available evidence, has greater efficacy than erlotinib. For this group of patients optimal therapy would be with pemetrexed and not erlotinib.

-for the subgroup of patients with squamous histology, erlotinib maintenance therapy has not been shown to have efficacy in terms of prolongation of survival.

The Delegate of the Minister outlined his consideration of the sponsor's review submission. The sponsor has submitted that non small cell lung cancer (NSCLC) is an aggressive and rapidly progressing disease and is the leading cause of cancer related deaths. This statement is supported by

a publication of the International Agency for Research on Cancer and another reference.[3] It also submits that "as many as 40%-50% of patients who derived benefit from first line chemotherapy are not fit enough to receive second line therapy". The figures 40% to 50% are, in the cited reference, derived from a consideration of only two clinical trials (Fidias et al., Ciuleanu et al).[4,5] The Delegate of the Minister noted that the paper states that the rate of patients not receiving second line therapy in those studies is similar to the rate observed on recent Phase III first line trials of first line therapy and that the authors go on to comment on the heterogeneity of patients which "make it difficult to anticipate the optimal time to initiate and to select the patient population who will benefit from the immediate initiation of second line therapy." While the Delegate of the Minister was of the view that the sponsor's statement that "delaying therapy until after disease progression is not a viable option for this large group of patients as they may die or deteriorate before being eligible for treatment" does not capture such heterogeneity, the Delegate of the Minister did not dispute that there is a place for therapeutic options that have appropriate quality, efficacy and safety.

The sponsor's Section 60 submission narrative ("submission narrative") included a recitation of the design, efficacy and Quality of Life aspects of the SATURN clinical trial. The sponsor cites the European Medicines Agency's Assessment Report. The report of the results of the SATURN clinical trial, also described as study BO18192, constituted the clinical information submitted to TGA in support of the application. The Delegate of the Minister noted that at the time the TGA's reports of the evaluations of this clinical trial were considered by the ADEC, the sponsor had not disputed the findings in the evaluation reports. In its Pre-ADEC response, the sponsor did object to a proposal of the Delegate to include in the product information at the end of the section dealing with maintenance therapy, a statement along the following lines:

"There are no data available to determine whether use of erlotinib as first line maintenance therapy is associated with superior outcomes compared to use of the drug as second line therapy when disease progression occurs."

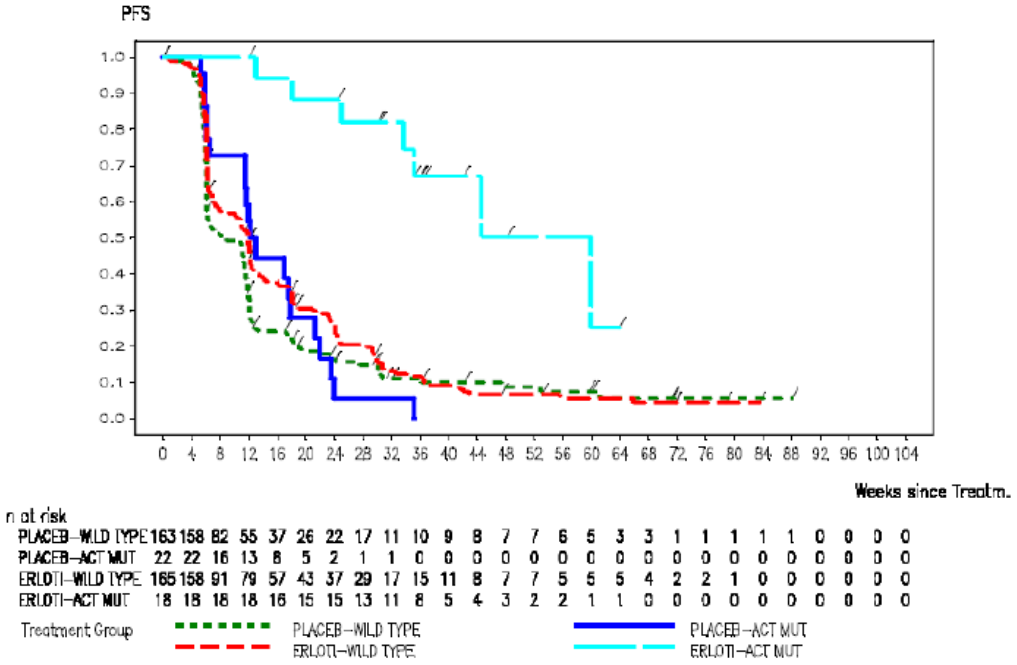
That objection does not dispute the outcomes of the TGA's evaluations of study BO18192. Importantly, the submission narrative does not mention the finding in study BO18192 of an important difference in PFS between subjects with EGFR activating mutation status (HR: 0.09; 95%CI 0.03; 0.25) and EGFR wild-type mutation status (HR: 0.81; 95%CI 0.64; 1.02). The difference in efficacy is shown in Figure 3.

[3] Stichcombe TE, Socinski MA. Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. J Thoracic Soc 2009; 4: 243-50.

[4] Fidias P, Dakhil S, Lyss A, et al. Phase III study of immediate versus delayed docetaxel after induction therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer: updated report with survival. J Clin Oncol 2007; 25: LBA7516.

[5] Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374: 1432-40.

Figure 3: Kaplan-Meier Curve of PFS by Study Treatment and EGFR Mutation Status



The submission narrative and the TGA's first clinical evaluation report both reflect that in the pre-defined parameters for assessment of Quality of Life, there were no significant improvements demonstrated in the group exposed to erlotinib. The submission narrative includes reference to some Quality of Life benefits of erlotinib found by post hoc analyses. These benefits were also alluded to in the sponsor's Pre-ADEC response when it stated "There was no adverse effect on quality of life while alleviating NSCLC-associated symptoms like pain, analgesic use, dyspnoea or cough."

The submission narrative addresses the SATURN efficacy results in the context of previous improvements in treatment. The sponsor supports the opinion that patients with advanced NSCLC should be treated in the first line with the administration of platinum-based chemotherapy by the American Society of Clinical Oncology (ASCO) guidelines 1997 and the results of a meta-analysis of clinical trials on which those guidelines were based. The submission narrative cites the updated 2009 ASCO guidelines recommending the use of platinum-based doublets as the first line therapy in advanced NSCLC and the meta-analysis on which the update was based. The Delegate of the Minister noted that the updated guideline does not provide guidance on the place of either pemetrexed or erlotinib in maintenance therapy ("the immediate initiation of second line chemotherapy before disease progression"). To the contrary, the guideline is explicit that this issue is to be the subject of future consideration. It was unclear to the Delegate of the Minister how the sponsor has made the transition from the citation of the updated guideline to the immediately following statement of opinion that "The magnitude of the efficacy benefit observed in the SATURN trial is clinically significant and in line with previously reported benefits of regimens that had a considerable impact on the treatment paradigm for NSCLC patients."

The submission narrative discusses the safety results of the SATURN study. The narrative does not mention the possible uncommon association between erlotinib administration and ILD noted in the first clinical evaluation. Otherwise, the narrative is consistent with the TGA evaluation of safety.

The submission narrative notes the fact that erlotinib for maintenance therapy of NSCLC has been approved recently by the European Medicines Agency and the United States Food and Drug Administration, based on the same information as submitted in Australia. The approval in the United States has occurred despite a recommendation to the contrary by the Oncologic Drugs Advisory Committee.

The submission narrative addresses the Delegate's statement that "An alternative therapy (pemetrexed) exists for patients with NSCLC with non-squamous histology, which has a favourable risk-benefit ratio, and which, on available evidence, has greater efficacy than erlotinib. For this group of patients optimal therapy would be with pemetrexed and not erlotinib." This statement was made by the Delegate in his decision letter (see above). The Delegate cited as the basis for this statement "the pemetrexed study, the clinical study report addendum." The Delegate of the Minister noted in the ratified minutes of the relevant ADEC meeting that it is recorded that "Critically, the improvements show no clear clinically significant benefit and the submission contained no comparison with either chemotherapy followed by second line chemotherapy on relapse, or chemotherapy followed by maintenance chemotherapy (pemetrexed), which would currently be regarded as optimal treatment in this condition."

In its submission narrative, the sponsor gives reasons why a comparison between the JMEN clinical study of pemetrexed as presented in the published report and the SATURN study might be misleading. This includes that the JMEN trial had higher proportions of subjects known to respond better to chemotherapy (Asians, never smoked) and a lower proportion of subjects known to respond less well to chemotherapy (squamous cell tumours). The submission narrative cites two references, including Samet et al. to support that the population studied in the SATURN study was more representative of the overall population of advanced (Stage III/IV) NSCLC than the population studied in the JMEN study of pemetrexed.[6]

The submission narrative then provides two comparisons which the Delegate of the Minister did not find useful. The HRs for OS in the two studies are similar (SATURN 0.81; 95% CI 0.70,0.95; JMEN 0.79; 95% CI 0.65,0.95). This similarity does not make apparent the considerable differences in median OS between the two studies: SATURN – placebo 11.0 months, erlotinib 12.0 months versus JMEN – placebo 10.6 months; pemetrexed 13.4 months). A similar criticism may be made of the use solely of HRs to compare the OS of subjects with non-squamous tumours in the JMEN study and subjects with EGFR wild-type tumours in the SATURN study.

The submission narrative refers to data from an earlier clinical study of erlotinib and to data from the SATURN study submitted to TGA to support its claim that unlike pemetrexed, erlotinib has benefit in subjects with both squamous and adenocarcinoma NSCLC. The Delegate of the Minister accepted this claim with respect to the SATURN study.

The submission narrative notes that erlotinib is an oral therapy. The sponsor has submitted a reference to support its claim that patients have a strong preference for oral treatment over intravenous (IV) chemotherapy if the efficacy is comparable and the patient's safety and Quality of Life are not compromised. The Delegate of the Minister noted that the submitted reference relates to a study of patients with incurable cancer taking palliative chemotherapy. It is not a study of patients with NSCLC being treated with an expectation of increased survival. Notwithstanding this, the Delegate of the Minister accepted that patients may have a preference for oral therapy.

---

[6] Samet JM, Avilla-Tang E, Boffetta P, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res 2009; 15: 5626-45.

Having considered the information documented above, the Delegate of the Minister formed the view that erlotinib has been shown to have a small benefit in terms of PFS in the treatment of NSCLC. The Delegate of the Minister particularly noted that, based on small numbers of subjects (n=40), treatment with erlotinib appears to have a significant benefit in the subgroup of subjects with activating mutations of the EGFR gene. Efficacy in the EGFR wild-type subgroup appears to be considerably more marginal.

The Delegate of the Minister considered the adverse effects profile of erlotinib. Rash and diarrhoea are common and may on occasions cause serious adverse events. The TGA clinical evaluator has pointed to a concern about a possible association of erlotinib with ILD.

The Delegate of the Minister noted that erlotinib is an oral therapy, which some patients may see as an advantage.

The Delegate of the Minister formed the view that it is likely that the drug has a positive benefit risk balance in patients with EGFR activating mutations and that it would not be appropriate to deny this therapy to this group of patients in whom the drug may be efficacious as maintenance therapy. The Delegate of the Minister decided that this could be achieved by permitting the extension of indications but requiring the inclusion of clear information about those patients most likely to benefit, as part of the approved indications and in the product information. The Delegate of the Minister decided that the issue of a possible association with ILD can be dealt with by requiring the Australian sponsor to commit to post-marketing pharmacovigilance similar to that already required in Europe.

The Delegate of the Minister noted that the ADEC recorded concern that there are no data available to determine whether use of erlotinib as first line maintenance therapy is associated with superior outcomes compared to use of the drug as second line therapy when disease progression occurs. The Delegate of the Minister also expressed a concern that the information currently available about superior efficacy in those with EGFR activating mutations is based on small numbers of such patients. The Delegate of the Minister decided that these concerns can be met by requiring the Australian sponsor to conduct and report to TGA the same investigations of feasibility and conduct of studies as have been committed to by its associated companies in Europe and the United States of America.

For these reasons, the Delegate of the Minister decided to substitute the decision below for that made by the Delegate of the Secretary:

"The application to extend the approved indications for erlotinib (Tarceva) tablets 25, 100 and 150 mg should be approved for the following indication:

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)."

The Delegate of the Minister was satisfied of the safety and efficacy of erlotinib (Tarceva) tablets 25 mg, 100 and 150mg for the substituted indication under certain conditions which include:

1. The product information must be modified as directed by the Delegate of the Minister to include specific information on efficacy and how it is influenced by tumour characteristics and updated information on OS

2. The sponsor must include in each Periodic Safety Update Report specific information on the ongoing pharmacovigilance, including use of guided questionnaires, of interstitial lung disease and of liver injury and must use those guided questionnaires in Australia as part of its pharmacovigilance on this product.

3. The sponsor must provide to the TGA in not more than two months after provision to the European Medicines Agency the results of its commitments to that agency, that is:

- to assess the feasibility of investigating the relative benefits of treatment with Tarceva prior to progression and post-progression in NSCLC, and if feasible and agreed between the Medicine Authorisation Holder (MAH) and CHMP, to conduct such an investigation, and

- to provide information to optimize therapy in patients with EGFR activating mutation-positive tumours by:

1) a submission of currently available data and

2) Submission of the Clinical Study Report from the Phase III on-going study (EURTAC: Phase III, Multicenter, Open-label, Randomised Study of Erlotinib (Tarceva) Treatment Versus Chemotherapy in Patients with Advanced Non-small-cell Carcinoma of the Lung Who Present Mutations in the Tyrosine Kinase (TK) Domain of Epidermal Growth Factor Receptor (EGFR)),

4. The sponsor must provide to the TGA in not more than two months after provision to the United States Food and Drug Administration the Clinical Study Report of the following study for which a commitment has been given to the FDA - "A randomized controlled trial in patients with histologically documented, advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have not experienced disease progression or unacceptable toxicity during chemotherapy with 4 cycles of platinum-based chemotherapy, comparing erlotinib as maintenance therapy with erlotinib at progression. The primary endpoint should be overall survival. This will be a trial to determine which is superior, erlotinib maintenance or erlotinib at progression. Regarding biomarkers, all eligible patients should have known EGFR by IHC status and EGFR mutation status. Final Report Submission date: December 2015."

Attachment 1. Product Information

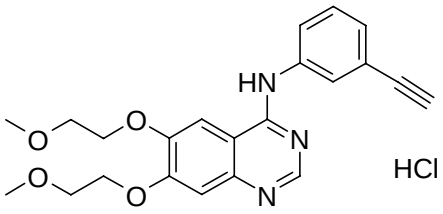
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

NAME OF THE MEDICINE

TARCEVA®

Erlotinib hydrochloride

CAS Registry Number: 183319-69-9



DESCRIPTION

TARCEVA (erlotinib hydrochloride) is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR, also known as HER1) tyrosine kinase inhibitor. Erlotinib, the active ingredient of TARCEVA, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)- 6,7- bis(2- methoxyethoxy)- 4- quinazolinamine.

Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4$. HCl and a molecular mass of 429.9. The molecule has a pK_a of 5.42 at 25ºC. Erlotinib hydrochloride is an off-white to pale yellow powder, it is sparingly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

Aqueous solubility of erlotinib hydrochloride is dependent on pH, with increased solubility at a pH < 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2.

TARCEVA tablets are available in 3 dosage strengths containing erlotinib hydrochloride equivalent to 25 mg, 100 mg or 150 mg of erlotinib and the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycollate, sodium lauryl sulfate and magnesium stearate. The film coating contains hypromellose, hydroxypropylcellulose, macrogol 400 and titanium dioxide. The printing ink contains iron oxide yellow CI 77492 (25, 100 and 150 mg tablets), iron oxide black CI77499 (100 and 150 mg tablets) and iron oxide red CI77491 (150 mg tablets).

PHARMACOLOGY

Pharmacodynamics
Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR tyrosine kinase with nanomolar potency; HER1/EGFR is expressed on the cell surface of normal cells and cancer cells of epithelial origin. However, the mechanism of antitumour action of erlotinib is not fully characterised. Erlotinib has been demonstrated to inhibit proliferation and/or induce apoptosis in human cancer cell lines *in vitro* and to inhibit the growth of a variety of human tumour xenografts in nude mice. Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterised.

Pharmacokinetics
Absorption: Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of bioavailability of 59%. The exposure after an oral dose may be increased by food.

Following absorption, erlotinib is highly bound in blood, with approximately 95% bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein [AAG]).

Distribution: Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC] and 1 with laryngeal cancer) receiving 150 mg daily oral doses of TARCEVA, tumour samples from surgical excisions on day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1 185 ng/g of tissue. This corresponded to an overall average of 63% of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumours at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration of [^{14}C] labelled erlotinib in athymic nude mice with HN5 (head and neck carcinoma) tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabeled drug in tumours (approximately 73% of that in plasma) and most other tissues observed to coincide with the peak plasma concentration.

Metabolism: Erlotinib is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/ CYP3A5 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 – 95% of erlotinib metabolism is by the CYP3A4 enzyme. There are 3 main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays. They are present in plasma at levels that are < 10% of erlotinib and display similar pharmacokinetics to erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the faeces (> 90%), with renal elimination accounting for only a small amount of an oral dose.

Elimination: A population pharmacokinetic analysis in 591 patients receiving single agent TARCEVA (252 patients from Phase II studies A248-101, A248-1003, A248-1007 and OSI2288g; 339 patients from Phase III study BR.21) show a mean apparent clearance of 4.47

L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7 – 8 days. No significant relationships between predicted apparent clearance and patient age, body weight, gender and ethnicity were observed.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG were associated with a slower rate of erlotinib clearance, however, smokers had a higher rate of erlotinib clearance.

A second population pharmacokinetic analysis was conducted incorporating erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. This analysis demonstrated that covariates affecting erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

Following a 150 mg oral dose of TARCEVA (591 patients – see above), at steady state, the median time to reach maximum plasma concentration is approximately 4 hours with median maximum plasma concentration achieved of 1 995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentration is 1 238 ng/mL. Median AUC achieved during the dosing interval at steady state is 41.3 μg.h/mL.

Pharmacokinetics in Special Populations

Hepatic impairment: Erlotinib is primarily cleared by the liver. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 – 9) compared with patients with adequate hepatic function.

The pharmacokinetics of erlotinib and its o-demethylated metabolites OSI-420 and OSI-413 were assessed in 36 patients with advanced solid tumours after a single 150 mg oral dose. Twenty-one patients had adequate hepatic function (total serum bilirubin ≤ upper limit of normal (ULN) and AST/AST ≤ 1.5 x ULN) and 15 had moderate hepatic impairment (Child-Pugh score 7 – 9).

Erlotinib and metabolite exposures were similar in the two groups, with geometric mean AUCs of 29 and 27 μg.h/mL for erlotinib in adequate and impaired hepatic function respectively and 2.0 and 2.4 μg.h/mL for metabolites respectively. However, the confidence intervals of the ratios of the AUCs were wide, so it could not be concluded that exposures were equivalent. The C_{max} of erlotinib was significantly lower in moderate hepatic impaired patients compared with those with adequate hepatic function consistent with delayed T_{max}. The differences in C_{max} and T_{max} are not clinically significant.

Renal impairment: Erlotinib and its metabolites are not significantly excreted by the kidneys (less than 9% of a single dose is excreted in the urine). No clinical studies have been conducted in patients with compromised renal function.

Smokers: A pharmacokinetic study in healthy non-smoking subjects and healthy subjects who currently smoke has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. After a single 150 mg dose of erlotinib, the $AUC_{0\text{-infinity}}$ in smokers was about 1/3 of that in never/former smokers (n = 16 in each of the smoker and never/former smoker

arms). This reduced exposure in smokers is presumably due to induction of CYP1A1 in the lungs and CYP1A2 in the liver.

In the pivotal Phase III NSCLC trial (see CLINICAL TRIALS), smokers achieved a median erlotinib steady state trough plasma concentration of 0.65 μg/mL (*n* = 16) which was approximately 2-fold less than the former smokers or patients who had never smoked (1.28 μg/mL, *n* = 108). This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance.

In a Phase I dose escalation study in NSCLC patients who smoked, pharmacokinetic analyses at steady state indicated a dose proportional increase in erlotinib exposure when the TARCEVA dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Median steady state trough plasma concentration at a 300 mg dose in smokers in this study was 1.22 μg/mL (*n* = 17) compared with 0.38 μg/mL (*n* = 15) at 150 mg. (see DOSAGE AND ADMINISTRATION**;** Special Dosage Instructions**)**

CLINICAL TRIALS

Non-Small Cell Lung Cancer (NSCLC) – TARCEVA Monotherapy

First-line maintenance therapy

The efficacy and safety of TARCEVA as first-line maintenance therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (BO18192). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress during 4 cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive TARCEVA 150 mg or placebo orally once daily. The co-primary end-point of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms.

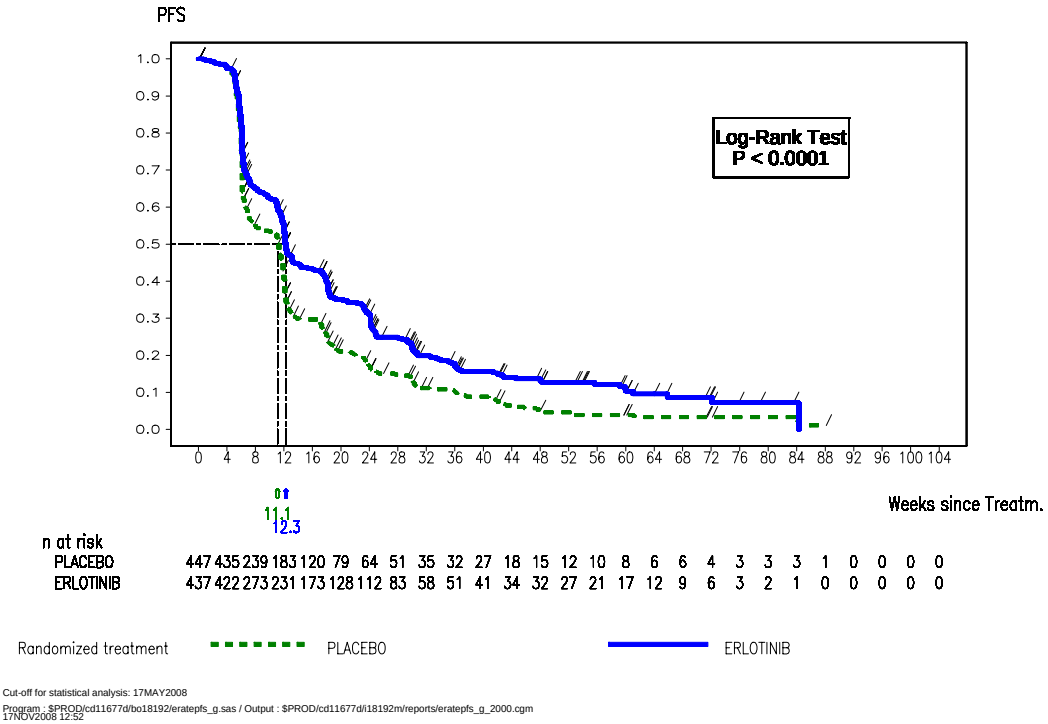
Table 1 shows the results of the primary PFS analysis in the intent-to-treat (ITT) population. The primary PFS analysis in all patients showed a hazard ratio for PFS in the TARCEVA group relative to the placebo group of 0.71. The median PFS was 12.3 weeks in the TARCEVA group and 11.1 weeks in the placebo group. The mean PFS was 22.4 weeks in the TARCEVA group compared with 16.0 weeks in the placebo group (see Figure 1).

Table 1: Study BO18192 Efficacy Results (ITT population)

	TARCEVA 150 mg (*n* = 438)	**Placebo (*n* = 451)**
Hazard ratio (95% CI)	0.71 ($p < 0.0001$) (0.62 – 0.82)	
Median PFS	12.3 weeks	11.1 weeks
Mean PFS (range)	22.4 weeks (0.1 – 84.3 weeks)	16.0 weeks (0.1 – 88.1 weeks)
6 months PFS rate	25%	15%

Disease Control Rate (CR, PR, SD>12 weeks)	40.8%	27.4%

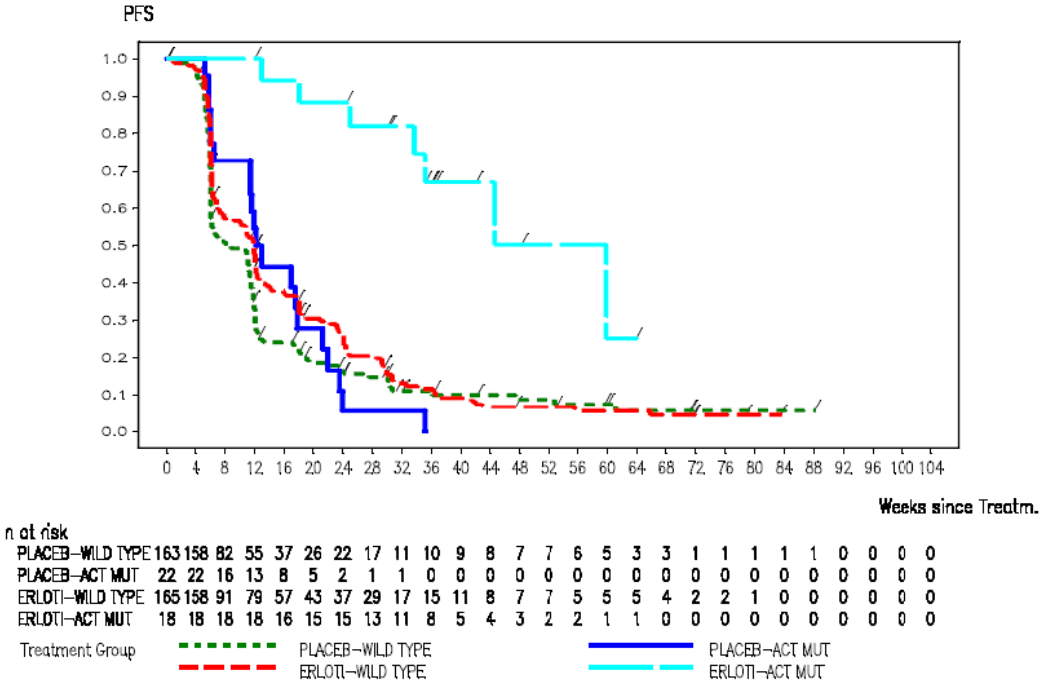
Figure 1: **Kaplan-Meier Curve for PFS of Patients by Treatment Group in Study BO18192**



The co-primary PFS analysis in patients with an EGFR IHC positive tumour was similar, with a hazard ratio (HR) of 0.69 (95% CI: 0.58 – 0.82; $p < 0.0001$). The mean PFS was 22.8 weeks in the TARCEVA group (range 0.1 – 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 – 88.1 weeks). The percentage of patients without progression at 6 months was 27% and 16%, respectively.

The efficacy was shown to be consistent across subgroups based on stratification and clinical factors. Benefit was also observed across biomarker subgroups independent of EGFR IHC, FISH, EGFR mutation or K-ras mutation status. Activating EGFR mutations have identified patients with the largest benefit (HR = 0.10; p < 0.0001) (figure 2).

Figure 2: Kaplan-Meier Curve of PFS by Study Treatment and EGFR Mutation Status (Activating Mutation and Wild Type)



Quality of life measurements suggested a similar effect from TARCEVA compared with placebo.

The benefit in PFS translated into statistically significant and clinically relevant benefit in overall survival (OS) (secondary end-point, HR = 0.81, see Table 2)

Table 2: Study BO18192 Efficacy Results, Overall Survival (ITT population)

	TARCEVA 150 mg (*n* = 438)	**Placebo (*n* = 451)**
Hazard ratio (95% CI)	0.81 (p = 0.0088) (0.70 – 0.95)	
Median Overall Survival	12.0 months	11.0 months

In the EGFR IHC positive population the median OS was 11.0 months in the placebo group and 12.8 months in the TARCEVA group (HR 0.77; 95% CI: 0.64 – 0.93; p = 0.0063).

Second-line and third-line therapy

The efficacy and safety of TARCEVA in second and third line therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (Study BR.21). This study was conducted in 17 countries, in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients, following disease progression, were randomised 2:1 to receive TARCEVA 150 mg (n = 488) or placebo (n = 243) orally once daily. Study endpoints included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), response rate, duration of response, progression-free survival (PFS) and safety. The primary end-point was survival.

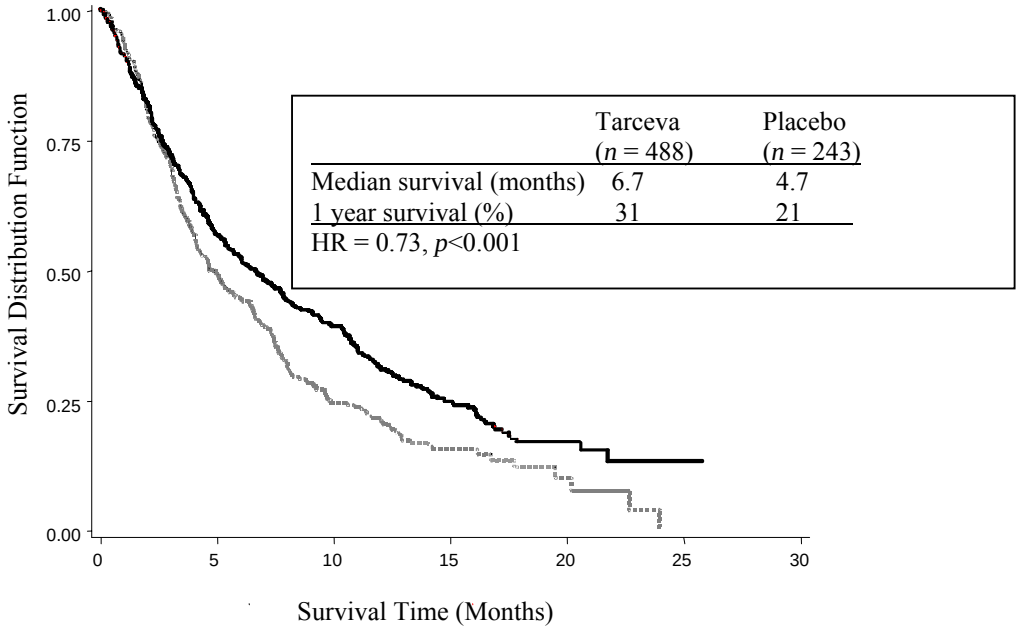
Patients were not selected for HER1/EGFR status, gender, race, smoking history or histologic classification. Demographic characteristics were well balanced between the two treatment groups (see Table 3). Approximately two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2 and 9% had a baseline ECOG PS of 3. Ninety-three percent and 92% of all patients in the TARCEVA and placebo groups respectively, had received a prior platinum-containing regimen and 36% and 37% of all patients respectively, had received a prior taxane therapy. Fifty percent of the patients had received only one prior regimen of chemotherapy.

Table 3: Study BR.21- Demographic and Disease Characteristics

Characteristics	TARCEVA *n* = 488		Placebo *n* = 243	
	n	**(%)**	***n***	**(%)**
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
Age (years)				
< 65	299	(61)	153	(63)
≥ 65	189	(39)	90	(37)
ECOG Performance Status				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Smoking History				
Never smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
Histological Classification				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
Number of prior regimens				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)

Survival was evaluated in the intent-to-treat population. The median overall survival improved by 42.5% and was 6.7 months in the TARCEVA group compared with 4.7 months in the placebo group (see Figure 3). The primary survival analysis was adjusted for the stratification factors as reported at the time of randomisation (ECOG PS, best response to prior therapy, number of prior regimens and exposure to prior platinum) and HER1/EGFR status. In this primary analysis, the adjusted HR for death in the TARCEVA group relative to the placebo group was 0.73 (95% CI: 0.60 – 0.87; $p = 0.001$). The percent of patients alive at 12 months was 31.2% and 21.5%, for the TARCEVA and placebo groups respectively.

Figure 3: **Kaplan-Meier Curve for Overall Survival of Patients by Treatment Group in Study BR.21**



The robustness of the overall survival result was examined in exploratory univariate analyses of a number of patient subsets formed according to stratification factors. The survival benefit with TARCEVA treatment was seen across patient subsets including prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomisation and geographic location. The HR in the TARCEVA group relative to the placebo group were less than 1.0, suggesting that the survival benefit from TARCEVA was robust across subsets. Of note, the survival benefit of TARCEVA was comparable in patients with a baseline ECOG PS of 2 – 3 (HR = 0.77) or a PS of 0 – 1 (HR = 0.73) and patients who had received one chemotherapy regimen (HR = 0.76) or two or more regimens (HR = 0.76).

A survival benefit of TARCEVA was also observed in patients who did not achieve an objective tumour response (by RECIST). This was evidenced by a HR for death of 0.82 among patients whose best response was stable disease or progressive disease.

Summarised in Table 4 are the results for study BR.21, including survival, time to deterioration of lung cancer-related symptoms and progression-free survival.

Table 4: Study BR.21- Efficacy Results

	TARCEVA *n* = 488	Placebo *n* = 243	*p*-value
Median survival	6.7 months	4.7 months	
Difference between survival curves			0.001
Hazard Ratio[a], mortality (erlotinib: placebo) 95% CI	0.73 0.60 - 0.87		0.001
Median time to deterioration in cough[c]	28.1 weeks	15.7 weeks	0.041
Median time to deterioration in dyspnoea[c]	20.4 weeks	12.1 weeks	0.031[b]
Median time to deterioration in pain[c]	12.1 weeks	8.1 weeks	0.040[b]
Median progression-free survival	9.7 weeks	8.0 weeks	<0.001

[a] adjusted for stratification factors and HER1/EGFR status; a value less than 1.00 favours TARCEVA (primary analysis)
[b] p-value adjusted for multiple testing
[c] from the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires

Symptom deterioration was measured using the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires. Baseline scores of cough, dyspnoea and pain were similar in the two treatment groups. TARCEVA resulted in symptom benefits by significantly prolonging time to deterioration in cough (HR = 0.75), dyspnoea (HR = 0.72) and pain (HR = 0.77) versus placebo. These symptom benefits were not due to an increased use of palliative radiotherapy or concomitant medications in the TARCEVA group.

The median PFS was 9.7 weeks in the TARCEVA group compared with 8.0 weeks in the placebo group. The HR for progression, adjusted for stratification factors and HER1/EGFR status, was 0.61 (95% CI: 0.51 – 0.73; $p < 0.001$). The percent of PFS at 6 months was 24.5% and 9.3% respectively, for the TARCEVA and placebo groups.

The objective response rate by RECIST in the TARCEVA group was 8.9% (95% CI: 6.4 – 12.0). The median duration of response was 34.3 weeks, ranging from 9.7 – 57.6+ weeks. Two responses (0.9%, 95% CI: 0.1 – 3.4) were reported in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 44.0% and 27.5% respectively, for the TARCEVA and placebo groups ($p = 0.004$).

Pancreatic Cancer – TARCEVA in Combination with Gemcitabine

The efficacy and safety of TARCEVA in combination with gemcitabine as a first line treatment was assessed in a randomised, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer (Study PA.3). Patients were randomised 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, Cycle 1 - days 1, 8, 15, 22, 29, 36 and 43 of an 8-week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4-week cycle (approved dose and schedule for pancreatic cancer according to gemcitabine product information). TARCEVA or placebo was taken orally once daily until disease progression or unacceptable toxicity. Study end points included overall survival, response rate and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival. A total of 285 patients were randomised to receive gemcitabine plus TARCEVA (261 patients in the 100 mg cohort and 24

patients in the 150 mg cohort) and 284 patients were randomised to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few observations were made for the 150 mg cohort to draw conclusions.

Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups except for a slightly larger proportion of females in the 100 mg TARCEVA plus gemcitabine arm (51%) compared with the placebo plus gemcitabine arm (44%). The median time from initial diagnosis to randomisation was approximately 1.0 month. Approximately half of the patients had a baseline ECOG performance status (PS) of 1 and 17% had a baseline ECOG PS of 2. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer (77% in the TARCEVA arm, 76% in the placebo arm).

Survival was evaluated in the intent-to-treat population based on follow-up survival data including 551 deaths. Results are presented for the 100 mg dose cohort (504 deaths) in Figure 2. The adjusted HR for death in the TARCEVA group relative to the placebo group was 0.82 (95% CI: 0.69 – 0.98;$p = 0.028$). The percentage of patients alive at 12 months was 23.8% in the TARCEVA group compared to 19.4% in the placebo group. The median overall survival was 6.4 months in the TARCEVA group compared with 6 months in the placebo group.

Figure 2: Kaplan-Meier curve for overall survival of patients in TARCEVA 100mg dose cohort by treatment group in Study PA.3

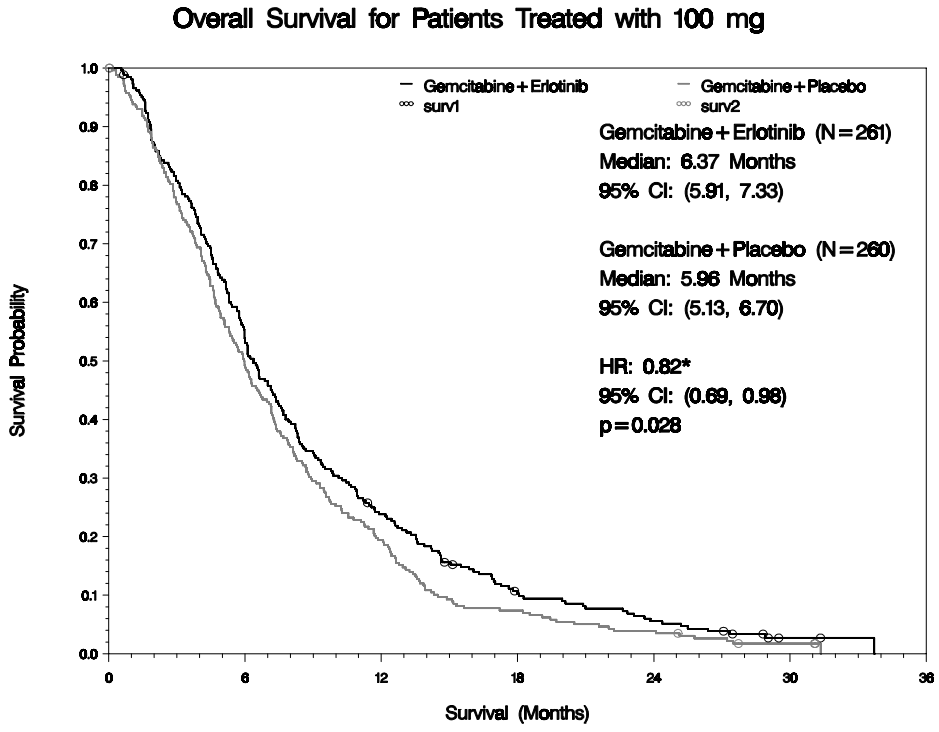


Table 5: Study PA.3 Efficacy Results

	TARCEVA 100 mg plus gemcitabine (*n* = 261)	Placebo plus gemcitabine (*n* = 260)	*p*-value
Median survival	6.4 months	6 months	
Hazard ratio, mortality (TARCEVA:placebo) (95% CI)	0.82 (0.69 – 0.98)		0.028
% patients alive at 12 months	23.8	19.4	

The median PFS was 3.81 months (16.5 weeks) in the TARCEVA group (95% CI; 3.58 – 4.93) compared with 3.55 months (15.2 weeks) in the placebo group (95% CI; 3.29 – 3.75; $p = 0.006$).

The median duration of response was 23.9 weeks, ranging from 3.71 – 56+ weeks. The objective response rate (complete response and partial response) was 8.6% in the TARCEVA group and 7.9% in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 59% and 49.4% respectively, for the TARCEVA and placebo groups ($p = 0.036$).

INDICATIONS

Non-small cell lung cancer:
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.

CONTRAINDICATIONS

TARCEVA is contraindicated in patients with severe hypersensitivity to TARCEVA or to any of the excipients.

PRECAUTIONS

Randomised controlled trials have demonstrated that TARCEVA combined with doublet, platinum-based cytotoxic chemotherapy in advanced NSCLC provides no added benefit over cytotoxic chemotherapy alone. TARCEVA should therefore only be used as monotherapy in advanced NSCLC, in patients who have previously received treatment with cytotoxic chemotherapy.

Interstitial Lung Disease (ILD)
Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumours. In the pivotal Phase III study BR.21 in NSCLC, the incidence of serious ILD-like events (0.8%) was the same in both the placebo and TARCEVA groups. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group versus 0.4% in the placebo plus gemcitabine-treated group. The overall incidence in TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating TARCEVA therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections. A causal association of ILD-like events to TARCEVA therapy has not been established.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, TARCEVA therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment initiated as necessary (see ADVERSE EFFECTS).

ECG Effects
In vitro studies indicate that TARCEVA blocks the hERG K^+ channel, producing 20% inhibition at concentrations 1.6 – 8 times higher than the peak free TARCEVA concentration in humans and therefore has the potential to inhibit cardiac action potential repolarisation. The clinical significance of these findings is unknown and adverse ECG effects have not been observed in human studies to date.

Diarrhoea and Dehydration
Diarrhoea has occurred in patients on TARCEVA and moderate or severe diarrhoea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia or vomiting associated with dehydration, TARCEVA therapy should be interrupted and appropriate measures should be taken to treat the dehydration.

Hypokalaemia, Renal Failure
There have been rare reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia, while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Lactose Intolerance
TARCEVA tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Hepatotoxicity, Hepatitis, Hepatic Failure
Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin) have been observed infrequently. These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

Rare cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered.

TARCEVA treatment should be interrupted or discontinued if changes in liver function are severe (see PRECAUTIONS; Hepatic Impairment and DOSAGE AND ADMINISTRATION; Special Dosage Instructions, Hepatic Impairment).

Gastrointestinal Perforations
Patients receiving TARCEVA are at an increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. TARCEVA should be permanently discontinued in patients who develop gastrointestinal perforation (see ADVERSE EFFECTS).

Bullous and Exfoliative Skin Disorders
Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see ADVERSE EFFECTS). TARCEVA treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliative conditions.

Ocular Disorders
Very rare cases of corneal perforation or ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment which are also risk factors for corneal perforation/ulceration. TARCEVA therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain (see ADVERSE EFFECTS).

Genotoxicity
TARCEVA has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration and mammalian cell mutation) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, TACEVA did not cause genetic damage.

Carcinogenesis
TARCEVA has not been tested for carcinogenic potential.

Effects on Fertility
TARCEVA did not impair fertility in male rats given doses that result in plasma drug concentrations similar to that of humans. TARCEVA administered at 10 mg/kg/day (1.5 times the clinical dose based on relative AUC) for 2 weeks prior to mating until day 7 of gestation affected ovulation in female rats, resulting in a reduction in the number of corpora lutea.

Use in Pregnancy – Category C
There are no adequate or well-controlled studies in pregnant women using TARCEVA.

When TARCEVA was administered during organogenesis, reduced foetal/birth weight and increases in the incidence of small, incompletely inflated lung lobes and incomplete or absent ossification were observed in rats at doses that resulted in plasma concentrations comparable to those in humans. In rabbits, foetal weight was reduced at plasma concentrations 1.5 times those of humans and the incidence of absent ossification was increased at doses producing 4.5 times the clinical exposure. Embryo/foetal lethality and/or abortion was seen in rats and rabbits given doses that result in plasma drug concentrations 4.5 – 6.5 times those of humans. Embryo/foetal toxicity was associated with maternal toxicity.

Women of childbearing potential must be advised to avoid pregnancy while on TARCEVA. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

Use in Lactation
It is not known whether TARCEVA is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving TARCEVA.

Paediatric Use
The safety and efficacy of TARCEVA has not been studied in patients under the age of 18 years.

Use in the Elderly
Of the total number of patients participating in the Phase III study BR. 21, 62% were less than 65 years of age and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups (see CLINICAL TRIALS). No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

Renal Impairment
The safety and efficacy of TARCEVA has not been studied in patients with renal impairment.

Hepatic Impairment
In view of the variability in pharmacokinetics, TARCEVA should be used with caution in patients with hepatic impairment and the dose tailored to individual patients (see Pharmacokinetics in Special Populations, Hepatic Impairment).

Patients with hepatic impairment are at increased risk of hepatic failure during treatment with TARCEVA. Therefore, close monitoring of hepatic function is recommended. TARCEVA treatment should be interrupted or discontinued if changes in hepatic function are severe (see PRECAUTIONS; Hepatotoxicity, Hepatitis, Hepatic Failure and DOSAGE AND ADMINISTRATION; Special Dosage Instructions, Hepatic Impairment).

The safety and efficacy of TARCEVA have not been studied in patients with severe hepatic impairment (total serum bilirubin > 3 x ULN). Use of TARCEVA in patients with severe hepatic impairment is not recommended.

Interactions with Other Medicines
TARCEVA is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/CYP3A5 and to a lesser extent by CYP1A2 and the pulmonary isoform CYP1A1. Potential interactions

may occur with medicines that are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) resulted in increased exposure to TARCEVA (86% in median TARCEVA AUC) and a 69% increase in maximum concentration (C_{max}) when compared to TARCEVA alone. When TARCEVA was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, TARCEVA exposure [AUC] and C_{max} increased by 39% and 17% respectively. Therefore, caution should be used when administering TARCEVA with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors such as ketoconazole, atazanavir, clarithromycin, erythromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin and voriconazole. In these situations, the dose of TARCEVA should be reduced if toxicity is observed.

Potent inducers of CYP3A4 increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg orally, 4 times a day for 7 days) resulted in a 69% decrease in the median TARCEVA AUC, following a 150 mg dose of TARCEVA, as compared to TARCEVA alone.

In another study, pre-treatment and co-administration of rifampicin with a single 450 mg dose of TARCEVA resulted in a decreased mean erlotinib exposure [AUC], which was 57.5% of a single 150 mg TARCEVA dose in the absence of rifampicin treatment. Therefore, caution should be used when administering TARCEVA with potent CYP3A4 inducers such as rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with TARCEVA and a potent CYP3A4 inducer such as rifampicin, an increase in dose to 300 mg should be considered while their safety is closely monitored and if well tolerated for more than 2 weeks, a further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Pre-treatment or co-administration of TARCEVA did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

The solubility of TARCEVA is pH dependent. TARCEVA solubility decreases as pH increases. Medicines that alter the pH of the upper gastrointestinal tract may alter the solubility of TARCEVA and hence its bioavailability. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the TARCEVA exposure [AUC] and C_{max} by 46% and 61% respectively. There was no change to T_{max} or half-life. Concomitant administration of TARCEVA with 300 mg ranitidine, a H_2-receptor antagonist, decreased TARCEVA exposure [AUC] and C_{max} by 33% and 54% respectively. Therefore, co-administration of TARCEVA with medicines that reduce gastric acid production should be avoided where possible. Increasing the dose of TARCEVA is not likely to compensate for loss of exposure. However, when TARCEVA was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg twice daily, TARCEVA exposure [AUC] and C_{max} decreased by 15% and 17% respectively. If patients need to be treated with such medicines, an H_2-receptor antagonist such as ranitidine should be considered and used in a staggered manner. TARCEVA must be taken at least 2 hours before or 10 hours after the H_2-receptor antagonist dosing.

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

The combination of TARCEVA and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of TARCEVA nor were there significant effects of TARCEVA on the pharmacokinetics of gemcitabine.

The impact of smoking on TARCEVA efficacy is not known, however, smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce TARCEVA exposure by 50 – 60% (see PHARMACOLOGY; Pharmacokinetics in Special Populations).

Ability to Drive or Operate Machinery
No studies on the effects on the ability to drive and use machines have been performed, however, TARCEVA is not associated with impairment of mental ability.

ADVERSE EFFECTS

Safety evaluation of TARCEVA is based on the data from more than 1200 patients treated with at least one 150 mg dose of TARCEVA monotherapy, and more than 300 patients who received TARCEVA 100 mg or 150 mg in combination with gemcitabine.

The incidence of adverse reactions reported with TARCEVA alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. The listed adverse reactions were those reported in at least 10% (in the TARCEVA group) of patients and occurred more frequently (≥ 3%) in patients treated with TARCEVA than in the comparator arm.

TARCEVA Monotherapy

The adverse reactions listed in Table 6 are based on data from the pivotal study BR.21 conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Patients were randomised 2:1 to receive TARCEVA 150 mg or placebo, taken orally once daily until disease progression or unacceptable toxicity.

The most frequent adverse reactions were rash and diarrhoea (any Grade, 75% and 54% respectively), most were Grade 1 – 2 in severity and manageable without intervention. Grade 3 or Grade 4 rash and diarrhoea occurred in 9% and 6% respectively in TARCEVA-treated patients and each resulted in study discontinuation in 1% of patients. Rash and diarrhoea diminished following discontinuation of TARCEVA. Dose reduction for rash and diarrhoea was needed in 6% and 1% of patients respectively. In study BR.21, the median time to onset of rash was 8 days and the median time to onset of diarrhoea was 12 days.

Table 6: Adverse reactions occurring more frequently (≥ 3%) in TARCEVA-treated group than in the placebo group and in ≥ 10% of patients in the TARCEVA group in study BR.21

	TARCEVA *n* = 485			Placebo *n* = 242		
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	40	22	96	36	22
Skin and subcutaneous tissue disorders						
Rash	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Gastrointestinal disorders						
Diarrhoea	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
General disorders and administration site conditions						
Fatigue	52	14	4	45	16	4
Metabolism and nutrition disorders						
Anorexia	52	8	1	38	5	<1
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
*Infections and infestations**						
Infection	24	4	0	15	2	0
Eye disorders						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0

* severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.

In another double-blind, randomised, placebo-controlled Phase III study (BO18192) conducted in 889 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified.

The most frequent adverse reaction seen in patients treated with TARCEVA in study BO18192 were rash and diarrhoea (any Grade, 49% and 20%, respectively), most were Grade 1 – 2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 6% and 2% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea

resulted in discontinuation of TARCEVA in 1% and < 1% of patients respectively. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively.

TARCEVA in Combination with Chemotherapy

The adverse reactions listed in Table 7 are based on the TARCEVA arm data from a controlled clinical trial (PA.3) where 259 patients with pancreatic cancer received TARCEVA 100 mg plus gemcitabine compared to 256 patients in the placebo plus gemcitabine arm.

The most frequent adverse reactions in study PA.3 in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue (73%), rash (69%) and diarrhoea (48%). In the TARCEVA plus gemcitabine arm, Grade 3 or Grade 4 rash and diarrhoea were reported in 5% of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days respectively. Rash and diarrhoea each resulted in dose reductions in 2% of patients and resulted in study discontinuation in up to 1% of patients receiving TARCEVA plus gemcitabine.

The TARCEVA 150 mg plus gemcitabine cohort (23 patients) was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

Table 7: Adverse reactions occurring ≥ 10% and more frequently (≥ 3%) in TARCEVA 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in Study PA.3

	TARCEVA plus gemcitabine *n* = 259			**Placebo plus gemcitabine *n* = 256**		
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	48	22	97	48	16
Skin and subcutaneous tissue disorders						
Rash	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
Gastrointestinal disorders						
Diarrhoea	48	5	<1	36	2	0
Stomatitis	22	<1	0	12	0	0
Dyspepsia	17	<1	0	13	<1	0
Flatulence	13	0	0	9	<1	0
Metabolism and nutrition disorders						
Weight decreased	39	2	0	29	<1	0

General disorders and administration site conditions						
Pyrexia	36	3	0	30	4	0
Fatigue	73	14	2	70	13	2
Rigors	12	0	0	9	0	0
Infections and infestations						
Infection*	31	3	<1	24	6	<1
Psychiatric disorders						
Depression	19	2	0	14	<1	0
Respiratory, thoracic and mediastinal disorders						
Cough	16	0	0	11	0	0
Nervous system disorders						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0

*severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.

Further Information on Adverse Reactions of Special Interest:

The following adverse reactions have been observed in patients who received TARCEVA monotherapy or TARCEVA 100 mg and 150 mg in combination with gemcitabine.

The following terms are used to rank the adverse reactions by frequency: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000) including isolated reports.

Very common adverse reactions are presented in Tables 6 and 7, adverse events in other frequency categories are summarised below:

Gastrointestinal disorders:
Gastrointestinal perforations have been reported uncommonly (in less than 1% of patients) with TARCEVA treatment, in some cases with a fatal outcome (see PRECAUTIONS). Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (see PRECAUTIONS; Interactions with Other Medicines) and some with concomitant NSAID administration.

Hepatobiliary disorders:
Liver function test abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) have been observed commonly in clinical trials of TARCEVA. In study PA.3, these occurred very commonly. They were mainly mild or moderate in severity, transient in nature or associated with liver metastases. Rare cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. (see PRECAUTIONS; Hepatotoxicity, Hepatitis, Hepatic Failure).

Eye disorders:
Corneal ulcerations or perforations have been reported very rarely in patients receiving TARCEVA treatment (see PRECAUTIONS).

Keratitis and conjunctivitis has been reported commonly with TARCEVA Abnormal eyelash growth including: in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported (see PRECAUTIONS).

Respiratory, thoracic and mediastinal disorders:
There have been uncommon reports of serious interstitial lung disease, including fatalities, in patients receiving TARCEVA for treatment of NSCLC and other advanced solid tumours.

Cases of epistaxis have also been reported commonly in both the NSCLC and the pancreatic cancer trials.

Skin and subcutaneous tissue disorders:
Rash has been reported very commonly in patients receiving TARCEVA and in general, manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing and/or use of sunscreen may be advisable. Skin fissures, mostly non-serious, were reported commonly and in the majority of cases were associated with rash and dry skin. Other mild skin reactions such as hyperpigmentation have been observed uncommonly (in less than 1% of patients).

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see PRECAUTIONS). Hair and nail changes, mostly non-serious, were reported in clinical trials, e.g. paronychia was reported commonly and hirsutism, eyelash/eyebrow changes and brittle and loose nails were reported uncommonly.

Cardiovascular disorders:
In the pivotal pancreatic cancer trial there was an excess of myocardial infarction/ischaemia (2.3% vs 1.2%) and cerebrovascular accidents (2.3% vs 0%) in the TARCEVA/gemcitabine group compared to the placebo/gemcitabine group.

Post-Marketing Experience

Skin and subcutaneous tissue disorders:
Hair and nail changes, mostly non-serious, have been reported uncommonly from post-marketing surveillance, e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails.

DOSAGE AND ADMINISTRATION

Non-Small Cell Lung Cancer

The recommended daily dose of TARCEVA is 150 mg taken at least one hour before or two hours after the ingestion of food. Treatment should be continued until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond disease progression is beneficial.

When dose adjustment is necessary, reduce in 50 mg steps.

Pancreatic cancer

The recommended daily dose of TARCEVA is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine Product Information for the correct dosage of gemcitabine in pancreatic cancer). Treatment should be continued until disease progression or unacceptable toxicity occurs.

Special Dosage Instructions

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see PRECAUTIONS; Interactions with Other Medicines).

Hepatic impairment
TARCEVA treatment should be interrupted or discontinued if;

- there is a doubling of total serum bilirubin and/or tripling of serum transaminases in patients with baseline hepatic impairment
- total serum bilirubin is > 3 x ULN and/or serum transaminases are > 5 x ULN in patients with normal pre-treatment values.
  (see PRECAUTIONS; Hepatic Impairment)

OVERDOSAGE

Single oral doses of TARCEVA up to 1000 mg in healthy subjects and up to 1600 mg given as a single dose once weekly in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose of 150 mg. In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment initiated. Treatment should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

TARCEVA 25 mg, 100 mg and 150 mg film-coated tablets are available in blisters containing 30 tablets.

TARCEVA 25 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 25' and logo in brownish yellow on one side.
TARCEVA 100 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 100' and logo in grey on one side.
TARCEVA 150 mg film-coated tablets are white to yellowish, round, biconvex tablets marked with 'TARCEVA 150' and logo in brown on one side.

Store below 30ºC.

Disposal of Medicines
The release of medicines into the environment should be minimised. Medicines should not be disposed of via waste water and disposal through household waste should be avoided. Unused or expired medicines should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

POISON SCHEDULE

Schedule 4 – Prescription only medicine.

TGA Approval Date: 15 October 2010