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ASSESSMENT REPORT
FOR
Tarceva

International non-proprietary name/Common name:
Erlotinib

Procedure No. EMEA/H/C/000618/II/0017

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. SCIENTIFIC DISCUSSION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer. Although there has been a gradual decrease in the incidence of NSCLC in men, it continues to increase in women. The treatment of NSCLC is determined by disease stage. Surgery continues to be the mainstay of treatment for early-stage and localised disease. Approximately 40% of patients with NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion.

The primary goals of therapy in patients with advanced and metastatic disease are palliative in essence, aiming at providing relief from symptoms and enhancing PFS and, if possible, survival. Platinum-based chemotherapy, when given as first-line therapy, modestly prolonged survival compared with best supportive care. The current standard of care for first-line treatment of advanced NSCLC consists of a platinum compound (cisplatin or carboplatin) combined with one of the newer chemotherapeutic agents (paclitaxel, pemetrexed, gemcitabine, docetaxel, vinorelbine and irinotecan). All the platinum-containing chemotherapies have similar efficacy.

Currently, bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology. Bevacizumab is administered in addition to the platinum-based chemotherapy for up to 6 treatment cycles after which bevacizumab is given as single agent maintenance therapy until disease progression. Furthermore, pemetrexed recently received a positive opinion from CHMP as single-agent maintenance therapy for patients with advanced, non-squamous NSCLC. The approval was based on a placebo-controlled phase III trial demonstrating a statistically significant difference in terms of the primary endpoint Progression Free Survival (PFS). The median PFS was 4.3 months in the pemetrexed group versus 2.6 months in the placebo group. In a secondary analysis of the independently assessed PFS, the observed median PFS was 4.04 months for the pemetrexed arm and 1.97 month for the placebo arm. The observed effect on PFS was supported by analysis of the secondary endpoint which was overall survival (OS), with median OS of 13.4 months associated to pemetrexed compared to 10.6 months for the placebo group. In a subgroup analysis in patients with non-squamous histology, the observed median OS with pemetrexed was 15.5 months versus 10.3 months in the placebo arm.

Tarceva (erlotinib) is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor (TKI). Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.
In vitro testing of erlotinib demonstrated a highly specific and potent inhibition of EGFR (IC50 = 2 nM). Subsequent in vivo experiments revealed EGFR inhibition in human tumour xenograft efficacy models, adequate bioavailability and pharmacokinetic properties. There were no serious toxicity issues that precluded its use as an antineoplastic agent.

Phase I studies in healthy subjects and cancer patients assessed the safety and pharmacokinetics of erlotinib at various dose levels and helped identify an appropriate dose (150 mg daily) for evaluation of antitumour activity in subsequent studies. Phase II studies of single-agent erlotinib in the treatment of advanced solid tumours other than NSCLC suggested antitumour activity in head and neck, ovarian, colorectal cancers, glioblastoma and hepatocellular carcinoma.

In a Phase II study in patients with Stage IIIb/IV NSCLC who had progressed despite platinum-based chemotherapy (Study A248-1007), a 12.3% objective response rate and a median overall OS of 8.4 months was demonstrated. These results compared favourably with data for chemotherapy (docetaxel) used in second-line therapy, as well as emerging data with similar EGFR agents.

BR.21 was subsequently initiated in collaboration with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). This study was conducted as a global, randomised , double-blind,

placebo-controlled study comparing erlotinib to best supportive care in patients with Stage IIIb/IV NSCLC after failure of at least 1 prior chemotherapy regimen. In BR.21, the use of erlotinib monotherapy in a second- and third-line setting was shown to provide a statistically significant and clinically meaningful prolongation of OS (HR=0.73, p=0.001, N=731) and PFS (HR=0.64, p< 0.001) in patients with advanced NSCLC. This pivotal study led to the initial approval of erlotinib for the treatment of patients with advanced NSCLC after failure of at least 1 prior chemotherapy regimen.

Use of erlotinib was also later extended to pancreatic cancer based on study PA.3 in combination with gemcitabine.

Based on the results of BR.21, 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 preclinical study in the NSCLC cell line *Calu1* 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 concomitantly with chemotherapy in the first-line setting in the TALENT and TRIBUTE studies, further exploratory analysis of the data from these studies showed that patients treated with erlotinib for more than 150 days (i.e., beyond the initial 4 cycles of chemotherapy) showed increased response duration compared with placebo (Gatzemeier, 2007 Herbst, 2005). These data suggested a possible benefit of single-agent erlotinib as a first-line maintenance therapy following chemotherapy as treatment for advanced NSCLC.

Study BO18192 (SATURN) was therefore designed as a Phase III, multicentre, randomised , double-blind, placebo-controlled study to evaluate the efficacy of erlotinib or placebo following 4 cycles of platinum-based chemotherapy in patients with Stage IIIb/IV NSCLC who had not experienced disease progression or unacceptable toxicity during chemotherapy. To investigate whether benefit was observed in the subpopulation of patients over expressing the target receptor EGFR, the study also assessed benefit in this subpopulation as a co-primary endpoint.

Tarceva was first approved in the EU on 19 September 2005 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen and also in combination with gemcitabine for the treatment of patients with metastatic pancreatic cancer.

This variation concerns an application for extension of the approved indications for Tarceva to include:
Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

1.1 Non-Clinical aspects

Environmental risk assessment (ERA)

With this application, the MAH submitted an expert report addressing the ERA for erlotinib.

No significant risk to sewage treatment plants, surface waters and groundwater has been identified from the use of erlotinib. Final conclusions concerning the effects of erlotinib on sediment organisms will be provided as a post-authorisation commitment.

1.2 Clinical aspects

1.2.1 GCP aspects/ Scientific Advice

The MAH stated that the primary study in this application, BO18192, was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong and South Africa), and the local laws and regulations of the countries in which the research was conducted.

No formal scientific advice was given by the CHMP for the indication "maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer who have not progressed on first-line chemotherapy".

1.2.2 Clinical pharmacology

In this application additional pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) information derived from Study BO18192, conducted in patients with stage IIIb or IV NSCLC following 4 cycles of platinum-based chemotherapy is presented (see Main Study).
The objectives of the current PK/PD analysis was to investigate the PK of erlotinib in NSCLC patients and furthermore to explore the potential relationship between exposure to erlotinib and measures of safety and efficacy.

Pharmacokinetics

In study BO18192 plasma samples were collected on all randomised patients. All patients entering in the study were to have five PK samples taken as follows:
• Baseline visit (Day 1 of the study): one sample was taken before the first dose of study medication was administered.
• Visit week 6: one pre-dose sample, one post-dose sample (time window between 3-5 hours).
• Visit week 12: one pre-dose sample, one post-dose sample (time window between 3-5 hours).
It should be noted, that the nature of this PK/PD dataset necessitated to disregard all patients who discontinued the study before week 6.

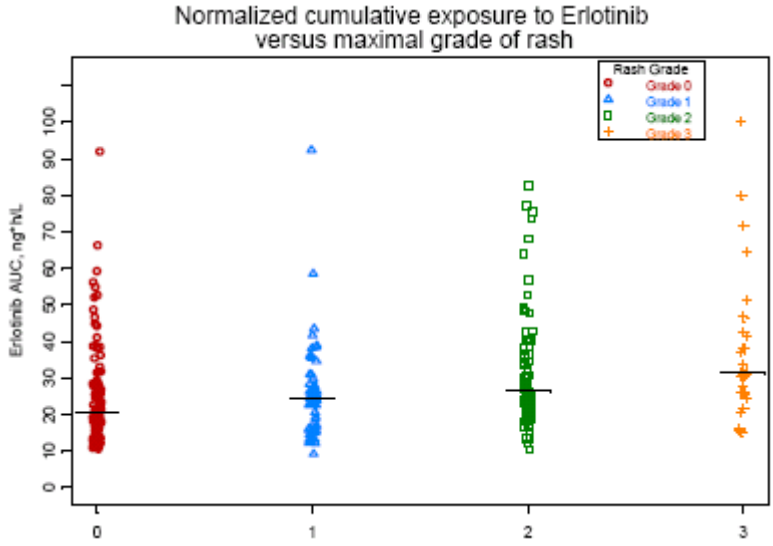
A total number of 308 patients were eligible for this PK/PD analysis. They were treated with erlotinib and had at least one measurable plasma concentration post dose. A total number of 882 plasma samples with measurable erlotinib concentrations were collected. From these 308 patients, 15 had measurable plasma concentrations at the baseline visit (before any drug intake), and 2 patients had implausible high plasma concentrations without any or long after any documented drug intake. These unexpected values were considered to be due to normal sampling or data recording errors. Therefore, these 17 subjects were excluded from the analysis. Data from 291 patients were available for the PK/PD analysis.
The final model included the effects of smoking habit (SMOK), gender (GDR), alpha-1-acid glycoprotein (AAG), albumin (ALBU), bilirubin (TBIL), and creatinine clearance (CRCL) on apparent clearance (CL/F) of erlotinib. The impact of the continuous covariates appears to be small compared to the observed overall variability.

CL/F appeared to be slightly higher in current smokers (≈20%) than in those who never smoked. Patients who had never smoked or who had quit smoking more than one year prior to randomisation were considered to be non-smokers for the use in the PK model.

Pharmacodynamics

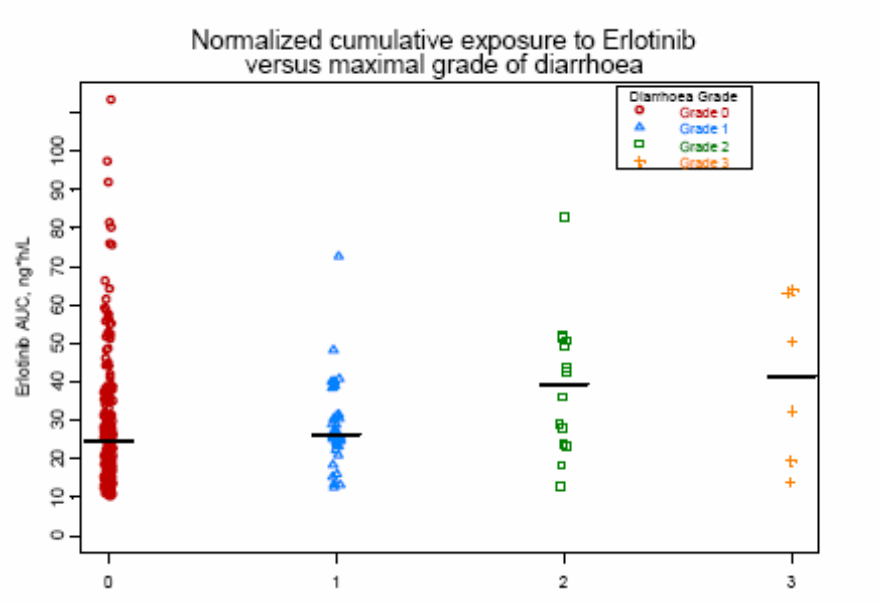
A graphical analysis of a potential relationship between exposure to erlotinib and selected parameters of safety and efficacy was performed. Parameters of safety were rash and diarrhoea as the known most common adverse events related to erlotinib. The range of exposure values observed across the different categories of rash and including those patients who did not develop rash appears to be similar (Figure 1). Higher grades of rash appeared to be associated with higher exposure to erlotinib.
However, at all rash grades 1 - 3, the range of exposure overlaps with the exposure range observed in patients without rash (grade 0).

Figure 1: Normalised cumulative exposure to Erlotinib by rash grade



Similarly for diarrhoea, the more severe grades 2 and 3 appeared to be associated with higher exposure to erlotinib (Figure 2). The small number of patients with higher grades of diarrhoea (14 patients with grade 2 and 6 patients with grade 3) might not allow drawing any firm conclusion, particularly as the ranges of exposure values in all diarrhoea grades are overlapping.

Figure 2: Normalised cumulative exposure to Erlotinib by diarrhoea grade



1.2.3 Clinical efficacy

- **Main study**

BO18192 study (SATURN)

BO18192 was a multi-center, double-blind randomised Phase III, placebo-controlled study designed to investigate the efficacy and safety of erlotinib in the maintenance setting following first-line platinum-based chemotherapy in patients with Stage IIIb or Stage IV NSCLC.

Methods

Study Participants

The target population for this study comprised patients with histologically documented, locally advanced or recurrent (Stage IIIb and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC.
A total of 1949 patients entered the chemotherapy run-in period. Of these, 889 were randomised to receive either erlotinib 150 mg/day (438 patients) or placebo (451 patients) after having completed 4 cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or progressive disease (PD). At the time of data cut-off on 17 May 2008 (after 749 events of progression or death), 98 patients were still on study drug (66 on erlotinib and 32 on placebo).
Patients were recruited at 110 centres in 26 countries (Europe, North America, South America and Asia-Pacific).

Key Inclusion Criteria

1. Histologically documented, locally advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC before chemotherapy.
2. Completion of 4 cycles of an acceptable, standard, platinum-based chemotherapy doublet without progression (i.e., CR, PR or SD).
3. ECOG PS of 0-1 before and after chemotherapy.
4. Life expectancy of at least 12 weeks.
5. Granulocyte count ≥ 1,500/mm3
6. Platelet count> 100,000/mm3
7. Haemoglobin ≥ 9.0g/dL,
8. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x upper limit of normal (ULN) in the absence of liver metastases or up to 5 x ULN in case of liver metastases.

Key Exclusion Criteria

1. Prior exposure to agents directed at the HER axis (eg, gefitinib, cetuximab, trastuzumab).
2. Prior chemotherapy or therapy with systemic anti-neoplastic therapy (eg, monoclonal antibody therapy) for advanced disease. Prior surgery and/or localized irradiation were permitted.
3. Serum creatinine > 1.5 ULN and/or creatinine clearance < 60 mL/min.
4. Patients who had undergone complete tumour resection after responding to platinum-based chemotherapy.
5. Any unstable systemic disease (including active infections, significant cardiovascular disease, [including myocardial infarction within the previous year], any significant hepatic, renal or metabolic disease) metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of study medication(s) or that might affect the interpretation of the results or render the patient at high risk from treatment complications.
6. Any other malignancies within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer).
7. Brain metastasis or spinal cord compression that had not yet been definitively treated with surgery and/or radiation; patients with previously diagnosed and treated central nervous system (CNS) metastases or spinal cord compression without evidence of stable disease(clinically stable imaging) for at least 2 months were also to be excluded.
8. Patients who were at risk (in the investigator's opinion) of transmitting human immunodeficiency virus (HIV) through blood or other body fluids.
9. Any inflammatory changes of the surface of the eye.

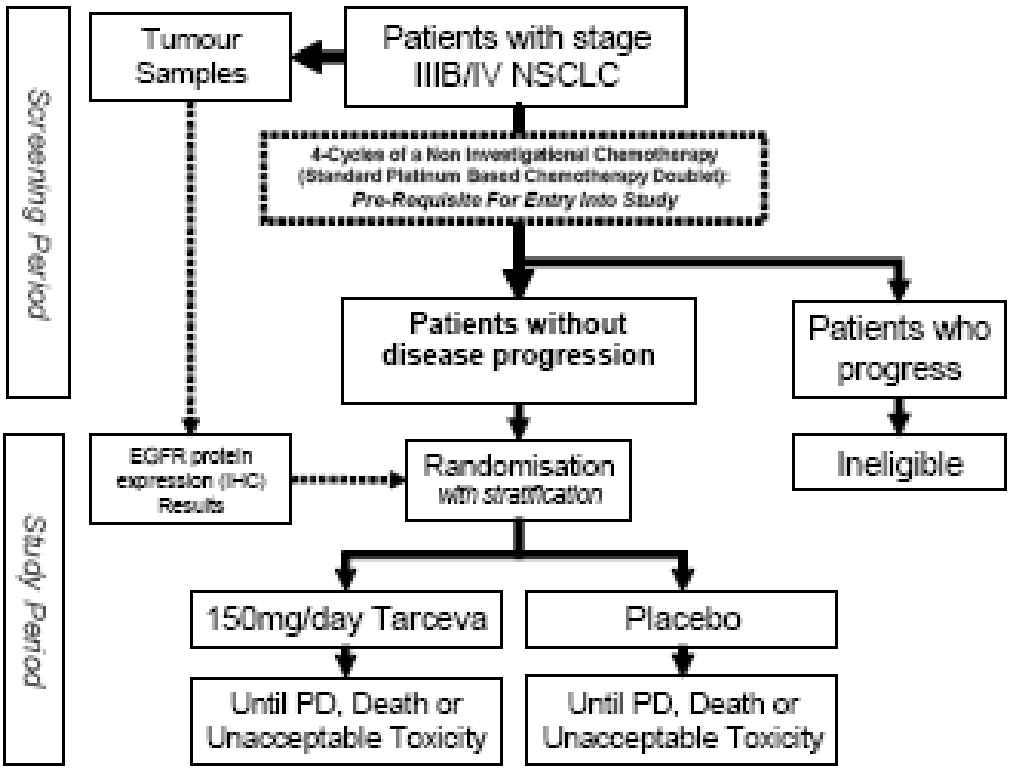
Treatments

Study B018192 comprised 2 components: (1) Screening phase/first-line platinum-based doublet chemotherapy, followed by (2) study drug treatment (blinded erlotinib/placebo).After eligibility

screening, patients with Stage IIIB or IV NSCLC completed 4 cycles of one platinum-based chemotherapy combination, with drugs, doses regimen and schema as specified by the protocol (cisplatin/paclitaxel (3-week schedule), cisplatin/gemcitabine (3- or 4-week schedule), cisplatin/docetaxel (3-week schedule), cisplatin/vinorelbine (3- or 4-week schedule), carboplatin/gemcitabine (3-week schedule), carboplatin/docetaxel (3-week schedule), carboplatin/paclitaxel (3-week schedule)). In the absence of unacceptable toxicity and/or disease progression (CR, PR or SD) eligible patients were randomised 1:1 to receive either erlotinib 150 mg/day or placebo until disease progression, unacceptable toxicity or death. Documentation of progression was assessed by investigators and verified by independent central review in a blinded fashion. Patients withdrawn from study medication were followed until death. A mandatory tumour sample was provided at screening within three weeks from starting chemotherapy. Tumour measurements (RECIST) were conducted at screening, baseline, then every 6 weeks until disease progression.

Erlotinib or placebo was administered daily, as a 150 mg tablet, in the morning at least 1 hour before or 2 hours after food intake with up to 200 mL of water. Dose reduction/interruption was allowed due to toxicity according to pre-specified protocol criteria. Guidelines for the management of rash and diarrhoea were also provided.

Figure 3: Design BO18192 (SATURN) study



Objectives

Primary objectives

Study BO18192 had two co-primary objectives:

- 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 the overall population.
- 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 immunohistochemistry (IHC).

Secondary objectives

The following secondary objectives were defined:

- to compare OS between the two treatment arms for all patients and for patients whose tumours are EGFR protein expression (IHC) positive.
- to compare PFS and OS between the two treatment arms in patients whose tumours are EGFR protein expression (IHC) negative.
- to perform exploratory evaluations of tumour-tissue and blood samples for biological or genomic determinants of outcome, including EGFR and Kirsten Rat Sarcoma 2 viral oncogene homolog (K-ras) mutational status and EGFR and HER2 expression status and of other molecules involved in the signal transduction pathway.
- to compare time to symptom progression between the two treatment arms.
- to evaluate the safety profile of administering erlotinib after standard platinum based chemotherapy in the treatment of NSCLC.
- to investigate by a population analysis approach the PK of erlotinib in the target population, including the influence of covariates and to provide post-hoc estimates of exposure. Exploration of the relationship between exposure to erlotinib and safety and efficacy parameters were performed.

Randomisation

Study BO18192 was a two-arm, randomised study. After completing 4 cycles of platinum-based doublet chemotherapy without disease progression, patients were randomised in a 1:1 ratio to receive either placebo or erlotinib 150 mg/day. Randomisation was stratified using an adaptive method (minimization) that ensured a balance between the treatment arms for the following factors: EGFR protein expression by IHC (positive vs. negative vs. undetermined), stage of disease at start of chemotherapy (IIIb vs. IV), Eastern Cooperative Oncology Group Performance Status (ECOG PS 0 vs. 1), chemotherapy regimen (gemcitabine/cisplatin vs. carboplatin/docetaxel vs. other), smoking status (current smoker vs. former smoker) and region (North America, South America, Western Europe, Eastern Europe, South East Asia and Africa). Central randomisation and drug pack number allocation were performed using an Interactive Voice Response System (IVRS).

Blinding

The study was double-blinded with the sponsor, investigators, and patients unaware of the treatment assignment of each patient. Unblinding of patients that had progressed was possible if (in the opinion of the investigator) the use of an EGFR-TKI was the only option for second- or third-line treatment. Unblinding was done through a third party (IVRS).

Statistical methods

The study was powered to the two primary analyses of PFS, conducted in the overall population and in patients who had EGFR IHC positive tumours, respectively. The PFS observed in the patients treated with placebo in the previously performed TALENT (BO16411) study, comparing erlotinib with placebo as first line therapy for advanced NSCLC, was used as the estimate for PFS from randomisation in the placebo arm. Overall, the study had a 5% significance level. The significance level was 3% for the analysis of the overall population and 2% for the EGFR IHC positive population. Following the interim analysis the significance levels to be used for the final analysis were 0.02934 for the Full Analysis Set (all randomised patients) and 0.01967 for the EGFR positive subset. For the secondary parameters and exploratory analysis further tests between the two treatment arms were performed. All tests were 2-sided at an alpha-level of 5%.
In order to detect a 25% improvement in the median PFS with erlotinib compared to placebo (HR=0.8) with 80% power at a 2-sided 3% significance level, 731 events (progression or death) were required. Assuming 18 months accrual, 6 months follow-up of last patient and a 5% dropout rate over 2 years, 427 randomised patients per arm were required.

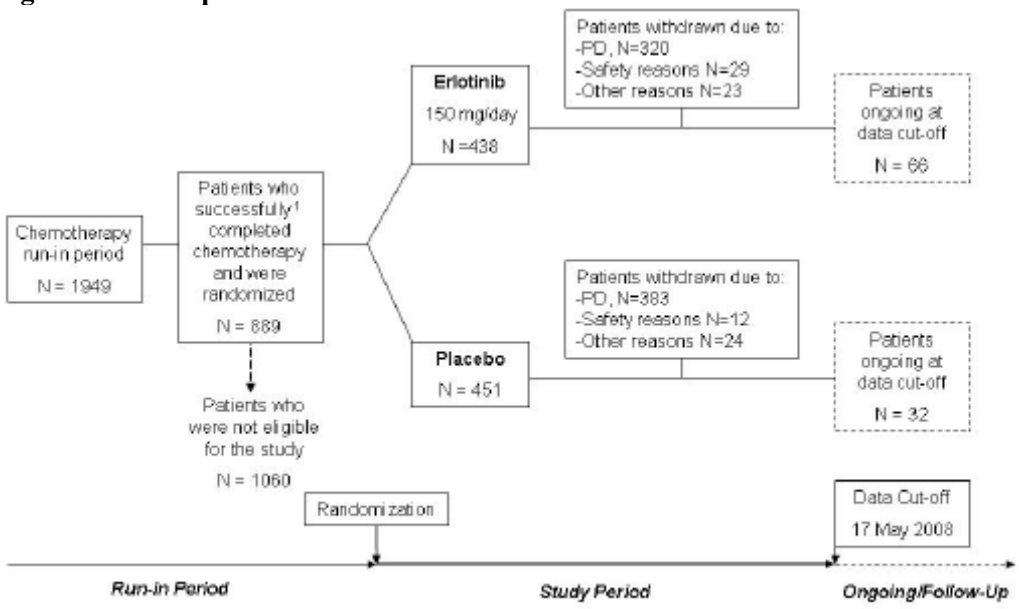
If 56% of patients were to dropout between start of chemotherapy and randomisation, due to disease progression or toxicity, etc, 971 patients per arm would need to be screened in order that 427 would be available for randomisation. Therefore, it was expected that approximately 2000 patients would have needed to be screened.
If 50% of patients had EGFR IHC positive tumours, this would lead to approximately 215 randomised patients per arm for testing the treatment difference in PFS for EGFR IHC positive population. The HR was expected to be lower in this subset of patients. A test of the difference in PFS for EGFR IHC positive population at a 2-sided significance level of 2% would have 85% power to detect a HR of 0.7 (360 events expected) and 66% power for a HR of 0.75 (365 events expected).
Additional considerations were done for the first secondary endpoint of OS, assuming a 10 month median survival in the placebo arm. In order to detect a 25% improvement in the median survival with erlotinib compared to placebo (HR=0.8) with 80% power at a 2-sided 5% significance level, 641 events (deaths) were required. Assuming 18 months accrual, 427 randomised patients per arm and 5% dropout over 3 years, 641 events were expected to occur at approximately 15 months after the last patient was randomised.
Nominal P-values (unadjusted for multiplicity) are presented in all tables.

Results

Participant Flow

The first patient entered the study on 29 March 2006. A total of 1949 patients (Figure 4) entered the chemotherapy run-in period, and subsequently a total of 889 patients that completed chemotherapy without progression and/or in absence of unacceptable toxicity were randomised 1:1 into the second part of the study, 438 patients in the erlotinb group and 451 patients in the placebo group. As of the 17 May 2008 cut-off date for the final analysis on PFS (after 749 events of progression or death), 98 patients were still on study drug (66 on erlotinib and 32 on placebo). Thus, a total of 791 patients (88.9%) in the Full Analysis Set (FAS) population had discontinued the study, 372 (84.9%) in the erlotinib group and 419 (92.9%) in the placebo group. The most frequent primary reason for study discontinuation was investigator determined progressive disease, which was higher in the placebo than in the erlotinib group (84.9% vs. 73.1%, respectively). Discontinuation due to an adverse event or death occurred in 6.6% of the patients in the erlotinb and 2.7% of the patients in the placebo group. Similar percentages of patients in the erlotinb and placebo groups discontinued study due to protocol violations or other reasons (refused treatment or failed to return). One patient who had been randomised to receive placebo, conducted chemical analysis of the blinded study drug, and subsequently stopped to take study medication and purchased erlotinib (independently of the study). This patient was excluded from the Per Protocol and the Safety Analysis Populations.

Figure 4: Participant flow



[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

Baseline data

The study population was similar to the general patient population with advanced NSCLC in several aspects (Table 1).

Table 1: Demographic and Baseline Characteristics Study BO18192

	Placebo N= 451	Erlotinib N= 438
Sex		
Female	113 (25%)	117 (27%)
Male	338 (75%)	321 (73%)
Age (years)		
Mean	59.7	59.8
Median	60.0	60.0
Min-Max	30-81	33-83
Race		
White	376 (83%)	370 (84%)
Black	1 (<1%)	3 (<1%)
Asian	66 (15%)	60 (14%)
Other	8 (<2%)	5 (<2%)
Region		
Africa	8 (2%)	8 (2%)
Eastern Europe	219 (49%)	207 (47%)
Western Europe	110 (24%)	112 (26%)
North America	20 (4%)	22 (5%)
South East Asia	94 (21%)	89 (20%)
ECOG PS		
0	145 (32%)	135 (31%)
1	306 (68%)	303 (69%)
Smoking Status		
Current smoker	254 (56%)	239 (55%)
Never smoked	75 (17%)	77 (18%)
Past smoker	122 (27%)	122 (28%)
Stage NSCLC		
IIIb	109 (24%)	116 (26%)
IV	342 (76%)	322 (74%)
Chemotherapy		
Cicplatin/paclitaxel	55 (12%)	52 (12%)
Cisplatin/gemcitabine	117 (26%)	118 (27%)
Cisplatin/docetaxel	24 (5%)	16 (4%)
Cisplatin/vinorelbine	32 (7%)	33 (8%)
Carboplatin/paclitaxel	83 (19%)	82 (19%)
Carboplatin/gemcitabine	130 (29%)	122 (28%)
Carboplatin/docetaxel	13 (3%)	13 (3%)
Histology NSCLC		
Squamous	194 (43%)	166 (38%)
PureAdenocarcinoma	176 (39%)	192 (44%)
Others	81 (18%)	80 (18%)

In general, biomarker subgroups were representative of the overall population, with a few exceptions (table 2).

Table 2 Biomarker status Study BO18192

	Placebo N= 451	Erlotinib N= 438
EGFR IHC		
Positive	313 (69%)	308 (70%)
Negative	59 (13%)	62 (14%)
Indeterminate	24 (5%)	16 (4%)
Missing	55 (12%)	52 (12%)
EGFR FISH (IUO)		
Positive	111 (25%)	121 (28%)
Negative	128 (28%)	128 (29%)
Indeterminate	64 (14%)	51 (12%)
Missing	148 (33%)	138 (32%)
EGFR Mutation Status		
Activating mutation	22 (5%)	18 (4%)
Resistance mutation	0 (0%)	1 (<1%)
Other mutation	2 (<1%)	6 (1%)
Wild Type	163 (36%)	165 (38%)
Indeterminate	48 (11%)	42 (10%)
Missing	216 (48%)	206 (47%)
K-Ras Mutation Status		
Classical mutation	41 (9%)	49 (11%)
Other mutation	1 (<1%)	0 (0%)
Wild Type	198 (44%)	205 (47%)
Indeterminate	30 (7%)	26 (6%)
Missing	181 (40%)	158 (36%)
EGFR Polymorphism		
High	204 (46%)	193 (45%)
Low	197 (44%)	190 (44%)
Indeterminate	2 (<1%)	5 (1%)
Missing	42 (9%)	44 (10%)

In general, treatment groups were well balanced with respect to previous diseases and medical procedures related and unrelated to NSCLC, and co-morbidities (which were present in 74% of patients in the placebo group compared with 69% in the erlotinib arm). The proportion of patients who received at least one concomitant treatment unrelated to NSCLC was slightly higher in the erlotinib compared with the placebo group (76% versus 69%, respectively). Moreover, during the randomised study period, a greater proportion of patients received treatment for AEs in the erlotinib group compared to the placebo group (60% versus 39% respectively). The most common classes of drugs given for AEs were corticosteroids (20% versus 7%, respectively, including topical steroids for rash), and opioid analgesics (12 and 13%, respectively). A significantly higher percentage of patients received antibiotics, antihistamines, antidiarrheals and dermatologic agents in the erlotinib group compared with the placebo group.

Outcomes and estimation

- *PFS in all randomised patients*

The analysis is based on 884 patients and 749 observed events (349 (79.9%) in the erlotinib and 400 (87%) in the placebo group); 135 patients without event at time of analysis were censored.

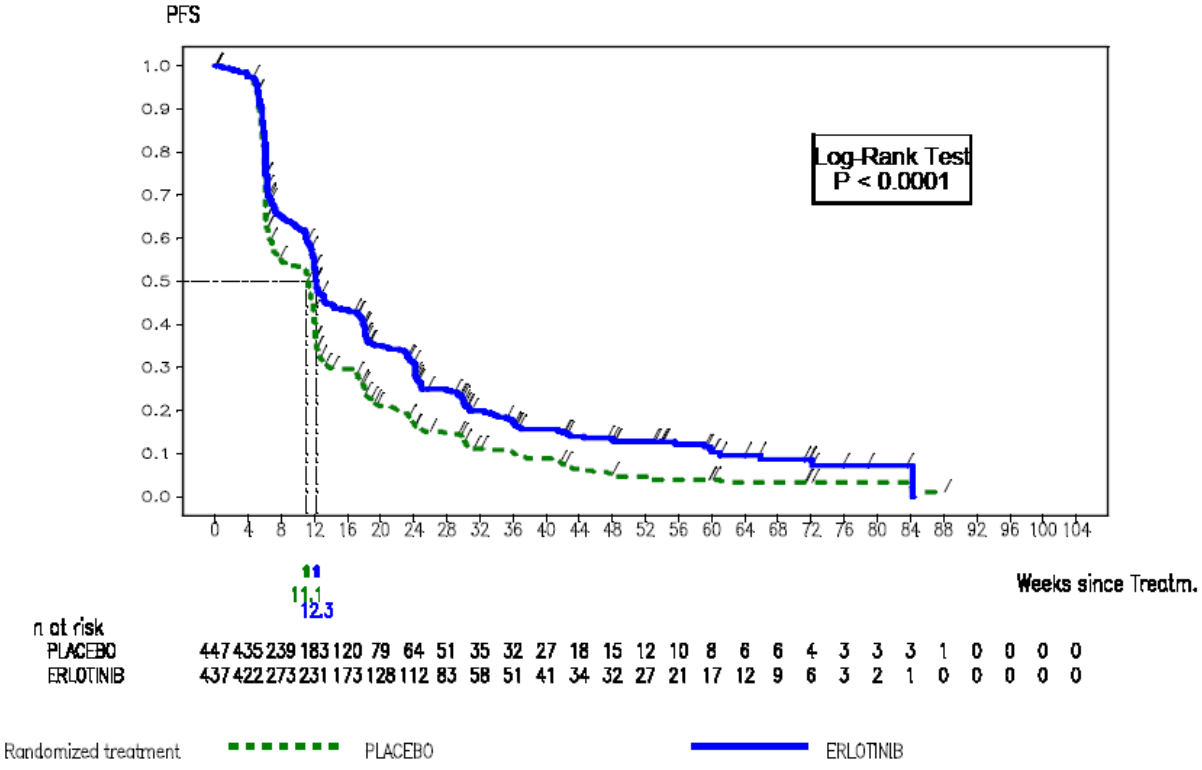
A statistically significant difference was observed for PFS in the Full Analysis Set (logrank p-value <0.001). The observed HR was 0.71, (95% CI: 0.62, 0.82) and the median PFS was 12.3 weeks *vs*. 11.1 weeks for erlotinib compared to placebo, respectively (Table 3, figure 5). The mean PFS was 22.4 weeks in the erotinib group compared with 16.0 weeks in the placebo group. Similar results were obtained when the PFS analysis was performed according to the independent central review assessment (HR: 0.71, 95% CI: 0.61, 0.84; concordance rate with investigator based PFS assessment: 78-82%) and for the Per Protocol population (HR: 0.72, 95% CI: 0.62, 0.83).

Table 3: Progression-Free Survival (FAS)

	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) (C9PFS)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2006

Figure 5: Kaplan-Meier Curve of Progression Free Survival (as adjudicated by investigators) (FAS)



- *PFS in patients with EGFR IHC positive tumours*

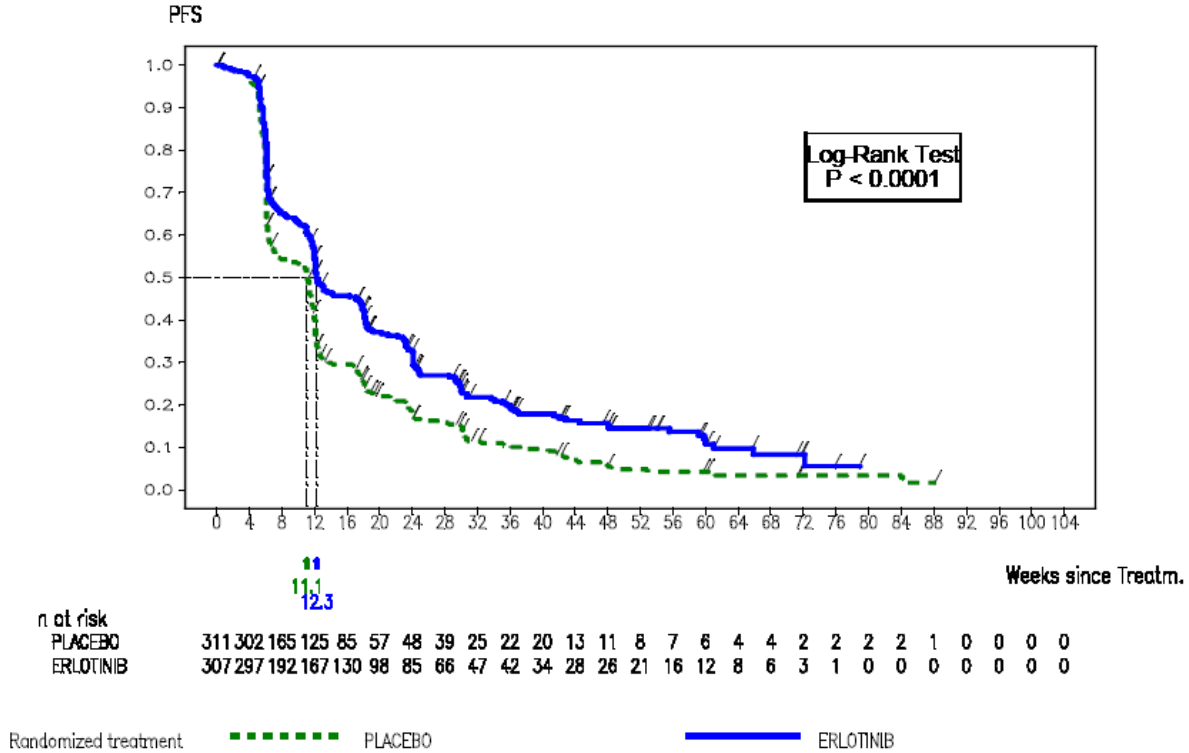
The analysis was based on 618 patients and 522 observed events (244 (79.5%) in the erlotinib and 278 (89%) in the placebo group); 99 patients without event at time of analysis were censored.
The median PFS was 12.3 weeks in the erlotinib and 11.1 weeks in the placebo group (logrank p<0.001, Table 4, figure 6). The HR was 0.69 (95% CI: 0.58, 0.82). The mean PFS was 22.8 weeks in the erlotinib group (range 0.1 to 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 to 88.1 weeks). The progression free survival rate at 6 months was 27% and 16%, respectively for erlotinib and placebo.

Table 4: Progression Free Survival (EGFR IHC Positive Population)

	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: 17MAY2006

Figure 6: Kaplan-Meier Curve of Progression Free Survival (EGFR IHC Positive Population)



Similar results were obtained when the PFS analysis was performed according to the independent central review assessment (HR: 0.66, 95% CI: 0.54, 0.80, p<0.0001) and for the Per Protocol population (HR: 0.69, 95% CI: 0.58, 0.82).

- *PFS results adjusted for prognostic factors*

The adjusted HR for PFS in the erlotinib group relative to placebo group was 0.70 (95 % CI 0.59 to 0.84, p<0.0001. Similar results were obtained for the EGFR IHC positive population (0.69[95 % CI 0.57 to 0.84] p=0003) (Table 5).

Table 5: Summary of Cox-Regression for PFS

		Covariate Effect*			Treatment Effect Adjusted for Covariate**		
Effect/Covariate	No. of Patients	Hazard Ratio	95% CI for Hazard Ratio	p-Value	Hazard Ratio	95% CI for Hazard Ratio	p-Value
Randomized Treatment Effect (unadjusted) [N=889]	884				0.71	[0.62;0.82]	<.0001
EGFR IHC (new reading): Negative vs Positive	884	1.16	[0.94;1.44]	0.1750	0.71	[0.62;0.82]	<.0001
EGFR IHC (new reading): Indeterminate vs Positive		1.02	[0.84;1.24]	0.8499			
Disease Stage: IIIB vs IV	884	0.86	[0.73;1.01]	0.0666	0.71	[0.62;0.82]	<.0001
ECOG PS: 0 vs. 1	884	0.92	[0.79;1.08]	0.3161	0.71	[0.62;0.82]	<.0001
Gemcitabine plus Cisplatin vs All Other	882	0.97	[0.83;1.14]	0.7242	0.71	[0.62;0.82]	<.0001
Smoking Status: Current Smoker vs Never Smoked	884	1.46	[1.19;1.80]	0.0003	0.72	[0.62;0.83]	<.0001
Smoking Status: Past Smoker vs Never Smoked		1.31	[1.04;1.65]	0.0198			
Region: South East Asia vs Eastern Europe	884	0.98	[0.81;1.19]	0.8190	0.71	[0.62;0.82]	<.0001
Region: Western Europe vs Eastern Europe		1.25	[1.04;1.48]	0.0145			
Region: North America vs Eastern Europe		1.35	[0.96;1.90]	0.0802			
Region: Africa vs Eastern Europe		1.15	[0.70;1.89]	0.5907			
Age: >=65 vs <65	884	0.81	[0.70;0.95]	0.0075	0.71	[0.61;0.82]	<.0001
Race: Asian vs White	884	0.78	[0.63;0.96]	0.0214	0.71	[0.62;0.82]	<.0001
Race: Other vs White		0.98	[0.54;1.78]	0.9416			
Gender: Male vs Female	884	1.23	[1.04;1.46]	0.0152	0.72	[0.62;0.83]	<.0001
Histology: Squamous Cell Carcinoma vs Adenocarcinoma	884	0.99	[0.85;1.16]	0.8874	0.71	[0.62;0.83]	<.0001
Histology: Other vs Adenocarcinoma		1.21	[0.98;1.50]	0.0779			
Previous Treatment: Surgery (Yes vs No)	884	0.90	[0.78;1.04]	0.1519	0.72	[0.62;0.83]	<.0001
Previous Treatment: Radiotherapy (Yes vs No)	884	1.20	[0.95;1.51]	0.1290	0.71	[0.61;0.82]	<.0001
Response to Previous Chemotherapy: CR/PR vs SD	881	1.06	[0.91;1.22]	0.4643	0.71	[0.62;0.82]	<.0001

Duration of PFS (primary analysis) [Days] (TTPFS) - Censoring: PFS Censoring (prim. ana.,1=PD/death) (CSPFS)
* Model that includes only the covariate
** Model that includes the covariate and treatment (no interaction term)
Cut-off for statistical analysis: 17MAY2008

Effect/Covariate	No. of Patients	Covariate Effect* Hazard Ratio	95% CI for Hazard Ratio	p-Value	Treatment Effect Adjusted for Covariate** Hazard Ratio	95% CI for Hazard Ratio	p-Value
Months Since First Diagnosis of NSCLC: >=12 vs <12	884	0.92	[0.70;1.22]	0.5746	0.71	[0.62;0.83]	<.0001
Involved Organs: Visceral Disease (Yes vs No)	884	1.36	[0.94;1.96]	0.1002	0.72	[0.62;0.83]	<.0001
Involved Organs: Bone (Yes vs No)	884	1.08	[0.87;1.35]	0.4758	0.71	[0.62;0.82]	<.0001
Involved Organs: Adrenal (Yes vs No)	884	1.02	[0.81;1.29]	0.8443	0.71	[0.62;0.82]	<.0001
Involved Organs: Lymphnodes (Yes vs No)	884	0.99	[0.85;1.15]	0.9076	0.71	[0.62;0.82]	<.0001
Number of Affected Organs: >=3 vs <3	884	1.23	[1.04;1.45]	0.0143	0.72	[0.62;0.83]	<.0001

Duration of PFS (primary analysis) [Days] (TTPFS) - Censoring: PFS Censoring (prim. ana.,1=PD/death) (CSPFS)
* Model that includes only the covariate
** Model that includes the covariate and treatment (no interaction term)
Cut-off for statistical analysis: 17MAY2008

- *OS in the FAS*

The cut-off date for the statistical analysis of these data was 17 May 2009. At that time point, 77.6% of patients in the placebo group and 68% of patients in the erlotinib group had an event (death). The updated OS analysis showed a median OS of 11.0 months in the placebo group compared with a median OS of 12.0 months in the erlotinib group. The HR was 0.81 (95% CI 0.70; 0.95), p=0.0088 (Table 6) (Figure 7).

Table 6: Summary of Overall Survival in the FAS

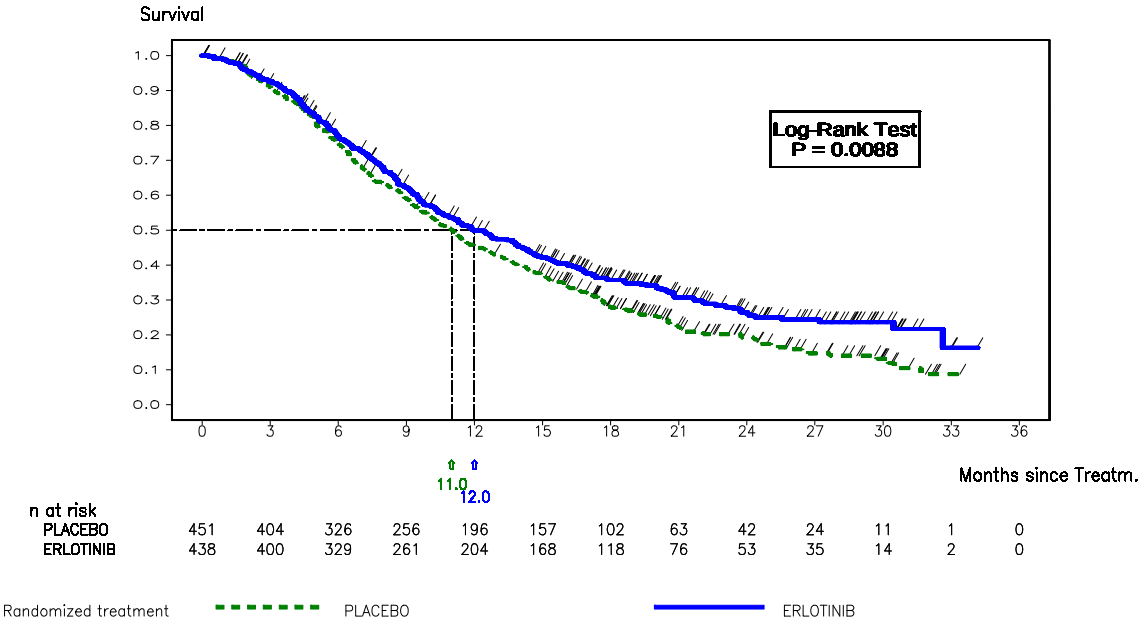
ettd_t_2000 Summary of Survival
Protocol(s): BO18192 (I18192V)
Analysis: Full Analysis Set

	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

Figure 7: Kaplan-Meier Curve of Overall Survival in the FAS

eratettd_g_2000_Kaplan-Meier Curve of Surviva
Protocol(S): BO18192 (I18192V)
Analysis: Full Analysis Set



n at risk

PLACEBO	451	404	326	256	196	157	102	63	42	24	11	1	0
ERLOTINIB	438	400	329	261	204	168	118	76	53	35	14	2	0

Randomized treatment PLACEBO ERLOTINIB

Cut-off for statistical analysis: 17MAY2009
Program : $PROD/cd11677d/bo18192/eratettd_g.sas / Output : $PROD/cd11677d/i18192v/reports/eratettd_g_2000.cgm
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The median OS benefit was 10.6 months and 12.5 months in the placebo and erlotinib groups, respectively in a supportive OS analysis censored by open-label erlotinib or second/further line TKI treatment.

- *OS in the EGFR IHC positive population*

A preliminary analysis of OS data conducted in the EGFR IHC positive population showed similar results to the overall population (median OS: 12.7 months in erlotinib and 12.1 months in placebo group; HR: 0.89, 95% CI: 0.70, 1.14, p=0.3638).
In line with the results of the overall population, the HR for the EGFR positive subgroup was 0.77 (95% CI 0.64; 0.93), p=0.0063. The median OS was 11.0 months in the placebo arm vs. 12.8 months in the erlotinib arm (N=621).

- *Time to Progression (TTP)*

Median TTP in the FAS was 12.3 weeks in erlotinib vs. 11.3 in placebo group. The HR was 0.70 (95% CI: 0.61, 0.82, logrank p<0.0001) (Table 7).

Table 7: Summary of Time to Progression (FAS)

	PLACEBO (N=451)		ERLOTINIB (N=438)
Patients included in analysis	447 (100.0 %)		437 (100.0 %)
Patients with event	389 (87.0 %)		332 (76.0 %)
Patients without event*	58 (13.0 %)		105 (24.0 %)
Time to event (weeks)			
Median#	11.3		12.3
95% CI for Median#	[8.1;11.9]		[12.0;14.1]
25% and 75%-ile	6.1;18.1		6.1;29.3
Range##	0.1 to 88.1		0.1 to 84.3
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.70	
95% CI		[0.61;0.82]	

- *Best Response Rate and Disease Control*

Only patients who had not progressed during the 4 cycles of platinum-based chemotherapy were eligible to enter the randomised treatment phase of the study. Response during blinded erlotinib/placebo treatment was assessed as discussed in table 8:

Table 8: Response assessment

Response at Baseline	Best Response	Response Upgrade
CR	Continued CR or PD	No
PR	SD or PR or CR or PD	Yes if best response = CR, No otherwise
SD	SD or PR or CR or PD	Yes if best response = PR or CR, No otherwise

In order to have best response as continued CR (for patients with CR at randomisation) the patient was required to remain tumour free for at least 6 weeks post baseline.

For patients with PR or SD at randomisation a best response of CR or PR required follow-up measurements meeting the criteria for CR or PR at 2 consecutive visits at least 4 weeks apart at any time post baseline. For best response SD follow-up measurements had to meet the SD criteria for at least 6 weeks post baseline.

Response assessments which were recorded as missing or NA at a visit were disregarded, as were responses occurring after a PD assessment. Patients with no tumour assessment post-baseline or missing best response were considered as non-responders and as patients with no response upgrade.

Best Response rate (CR or PR after randomisation) as assessed by the investigators was 11.9% in the erlotinib arm compared with 5.4% in the placebo arm (p=0.0006, 4 and 3 CRs respectively). The proportion of PR was higher in the erlotinib group (11.0% vs. 4.7% respectively) and the rate of SD was similar in both treatment groups (48.6% vs. 45.4%).

The proportion of response upgrade was 5.5% in the erlotinib group vs. 1.3% in the placebo group (p=0.0007).
Disease Control (as defined as the number of patients with CR, PR or SD as best overall response) was 60.6% in the erlotinib group vs. 50.8% in the placebo group (p=0.0035) and the percentage of patients with CR, PR or SD for more than 12 weeks was 40.8% in the erlotinib group vs. 27.4% in the placebo group (p<0.0001).

- *Quality of life* (QoL) *and related outcomes*

451 patients in the placebo group and 438 patients in the erlotinib group were included in the analysis of QoL and related endpoints. Completion rates of questionnaires were above 90% at almost all study visits and were similar in both treatment groups.
Time to symptom progression (defined as time from randomisation until a clinically meaningful decline (change of at least 3 points from baseline) in Lung Cancer Subscale (LCS) from baseline or death on study, whichever occurred first) was similar in both treatment groups (median 18.3 weeks in erlotinib and 17.6 in placebo arms; HR=0.91, 95% CI: 0.74, 1.12, p=0.3787), as well as time to deterioration in quality of life, defined as deterioration of at least 6 points from baseline in the total FACT-L score (median 12.6 weeks vs. 12.3 weeks, respectively, HR=0.96, 95% CI: 0.79, 1.16, p=0.6530).

In addition, time to deterioration in Trial Outcome index (defined as at least 6-point decline from baseline in the sum of PWB, FWB, LCS) was 18.1 weeks in the erlotinib vs. 18.9 weeks in the placebo arm (HR=1.06, 95% CI: 0.87, 1.31, p=0.5385).

Ancillary analyses

- *Efficacy in patients with stable disease (SD)*

Further to CHMP request, the MAH provided efficacy data of erlotinib as maintenance therapy for patients with stable disease (RECIST criteria version 1.0). Documentation of progression was verified by independent central review.

A summary of the distribution between treatment arms of the main clinical and molecular characteristic in the SD population that may have prognostic or predictive value is given in Table 9 and Table 10. In addition no imbalances were found between treatment arms when geographical, prior radiotherapy, subsequent systemic treatments and time to start of investigational treatment parameters were analysed.

Table 9: Summary of Clinical Characteristics in Patients with SD as Best Response to first-Line Chemotherapy

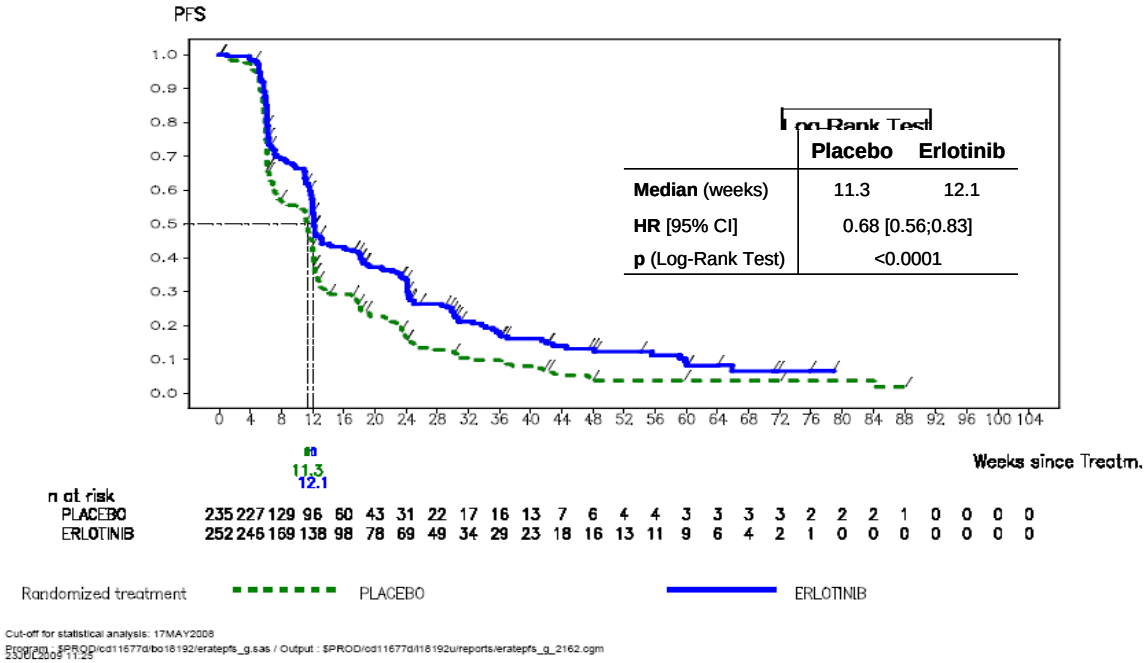
		Placebo N = 235	**Erlotinib N = 252**
Gender	Female	63 (27%)	62 (25%)
	Male	172 (73%)	190 (75%)
Age	Median	58.0	61.0
	Min-Max	30 – 81	33 - 82
Race	Oriental	35 (15%)	34 (13%)
	Non-Oriental	200 (85%)	218 (87%)
ECOG PS at Baseline	0	77 (33%)	70 (28%)
	1	158 (67%)	182 (72%)
Smoking Status	Current	125 (53%)	132 (52%)
	Past	62 (26%)	73 (29%)
	Never	48 (20%)	47 (19%)
Histology	Adenocarcinoma	112 (48%)	123 (49%)
	Squamous	93 (40%)	97 (38%)
	Large Cell	13 (6%)	6 (2%)
	Other	17 (7%)	26 (10%)
Stage	IV	182 (77%)	182 (72%)
	IIIB	53 (23%)	70 (28%)

Table 10: Summary of Biomarker Analysis in Patients with SD as Best Response to first-Line Chemotherapy

		Placebo N = 235	Erlotinib N = 252
Tumour Site	Metastasis	57 (24%)	57 (23%)
	Primary Tumour	178 (76%)	195 (77%)
EGFR IHC	Positive	164 (70%)	182 (72%)
	Negative	34 (14%)	36 (14%)
	Indet/Missing	37 (16%)	34 (14%)
EGFR FISH	Positive	54 (23%)	68 (27%)
	Negative	71 (30%)	84 (33%)
	Indet/Missing	110 (47%)	100 (39%)
EGFR Mutation Status	Activating Mutations	15 (6%)	15 (6%)
	Wild-Type	103 (44%)	114 (45%)
	Other/Indet/Missing	117 (50%)	123 (49%)
KRAS Mutation Status	Mutations	19 (8%)	30 (12%)
	Wild-Type	109 (46%)	118 (47%)
	Indet/Missing	106 (45%)	104 (41%)
EGFR Polymorphism	High	104 (45%)	104 (42%)
	Low	105 (45%)	115 (46%)
	Indet/Missing	22 (9%)	29 (12%)

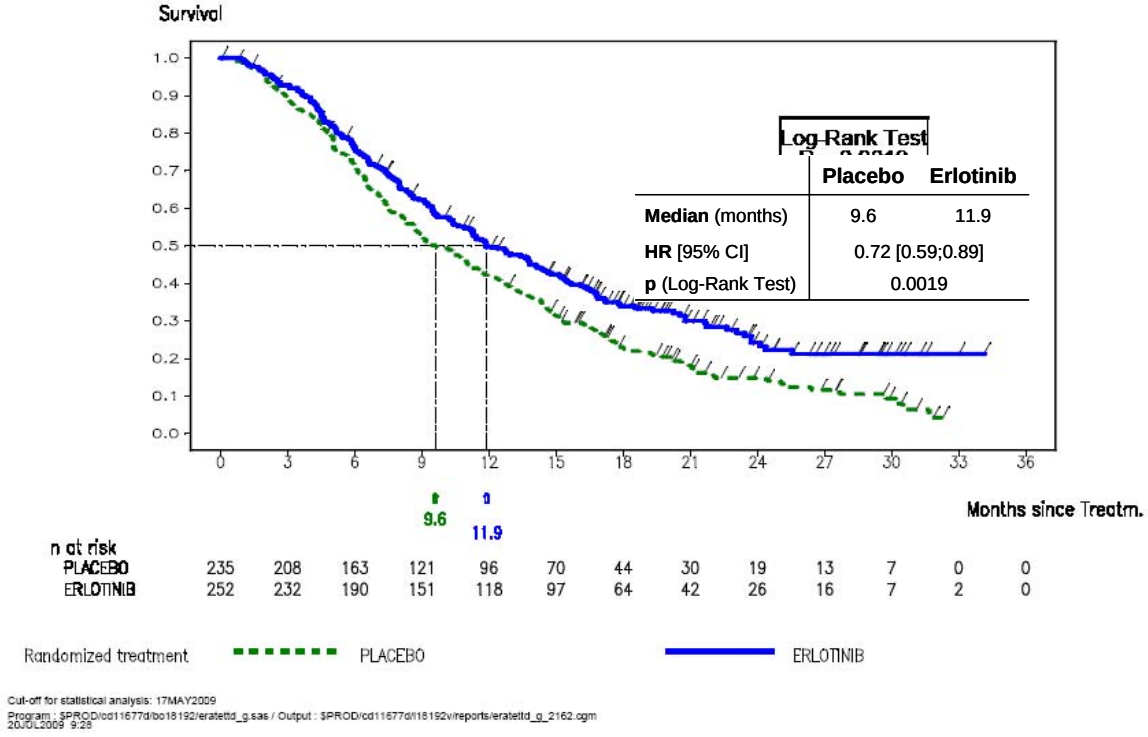
Following investigators' assessment the hazard ratio (HR) for the primary endpoint, progression free survival (PFS), according to stable disease (SD) as response to previous chemotherapy was 0.68 (95% CI 0.56 to 0.83, p<0.0001). Median PFS was 11.3 weeks in the placebo group versus 12.1 weeks in the erlotinib group (see Figure 8).

Figure 8: Kaplan-Meier Curve of PFS – Response to Previous Chemotherapy SD



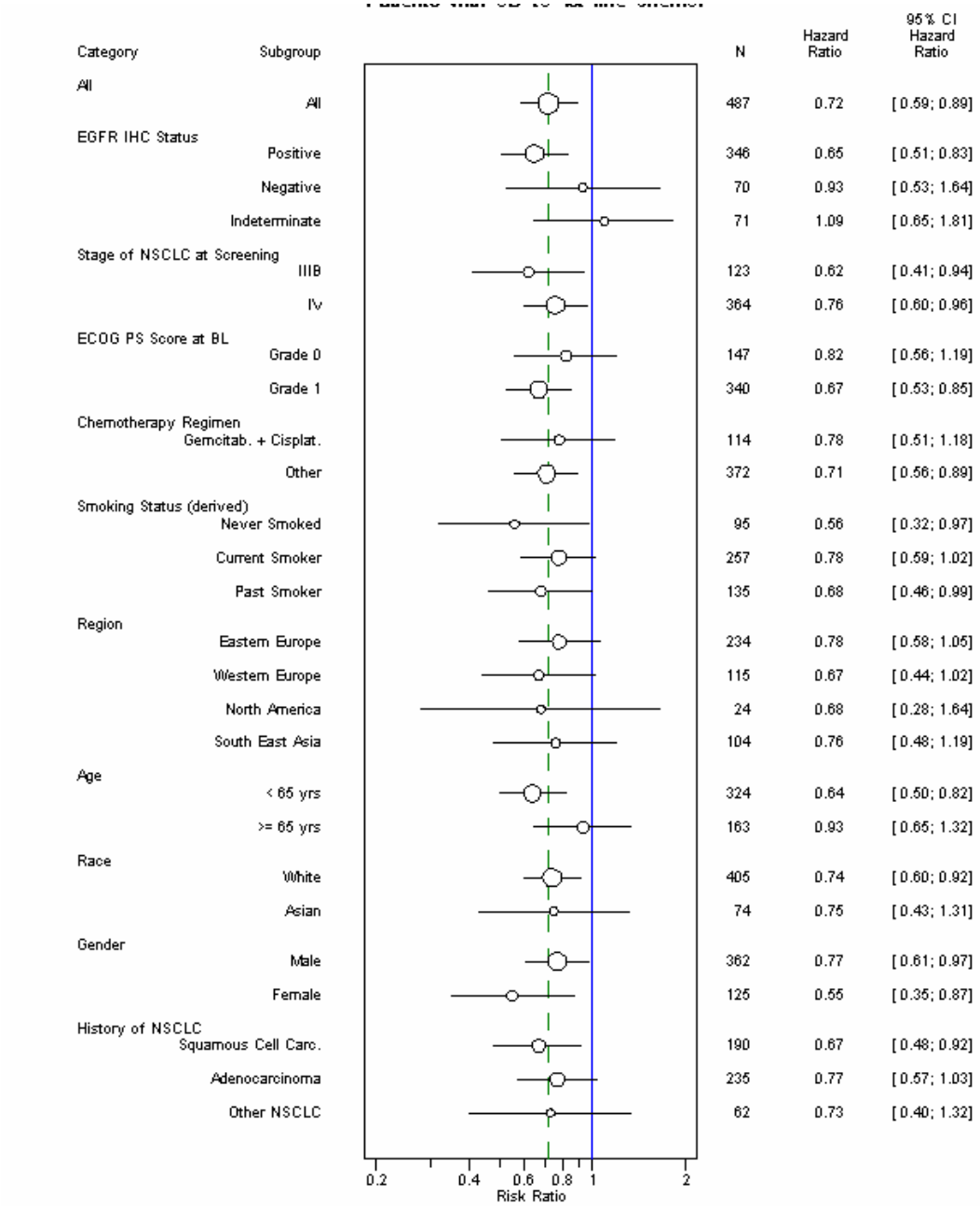
The HR for overall survival was 0.72 (95% CI: 0.59; 0.89; p=0.0019) with a median survival difference of 2.3 months (Figure 9).

Figure 9: Kaplan-Meier Curve of Survival – Response to Previous Chemotherapy SD (ITT Population)



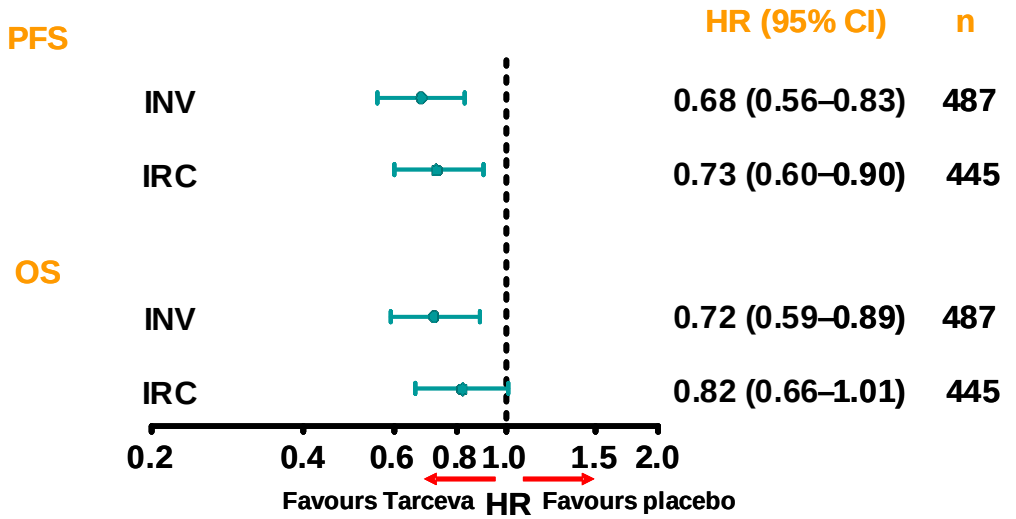
Subgroup analysis showed consistent OS difference across subgroups (see figure 10). All HRs were below 1.00, except for patients with EGFR IHC status 'indeterminate'.

Figure 10: Subgroup analyses of OS in patients with SD on 1st-line chemotherapy



The PFS and OS results for the SD population as defined by the IRC supported the results as assessed by the investigator (see figure 11). The central review and the investigator review assessed patients as SD according to RECIST version 1.0. According to the central review, 445 patients had SD as best response to first-line chemotherapy compared to 487 patients assessed as SD by investigator (INV). Randomization and primary efficacy analyses were based on INV assessment from baseline. The IRC assessment at baseline was post-hoc and retrospective and conducted to corroborate the pre-specified INV non-progression assessments at the point of randomization into the SATURN study. The IRC assessment lacked data from multiple patients, due to missing or non-readable scans, as well as the clinical information used for the INV baseline assessment.

Figure 11: PFS and OS among patients with SD after 1st-line chemotherapy: investigator and independent review



The time to symptom progression, time to deterioration in QoL and time to deterioration in Trial Outcome Index (TOI) were similar in both treatment groups (HR=0.92, 95% CI 0.70 to 1.22, p=0.5768; HR=0.97, 95% CI 0.75 to 1.26, p=0.8291; and HR=1.14, 95% CI 0.86 to 1.50, p=0.3534 respectively). The QoL results observed for the SD population are in line with those observed in the Full Analysis Set. In both cases, no deterioration in quality of life was observed for patients receiving treatment with erlotinib compared to those receiving only placebo.

- *PFS by biomarker subgroups*

Further to CHMP request, the MAH provided an updated description of the total number of tumour samples and the number of patients who were tested EGFR activating mutation positive in the SATURN study (Figure 10) and the results of PFS and OS for both the EGFR activating mutation positive and negative (EGFR WT) patients in the subgroup of patients with known mutational status in the SATURN study.

Figure: 12 Breakdown of Tissue Samples Obtained in SATURN

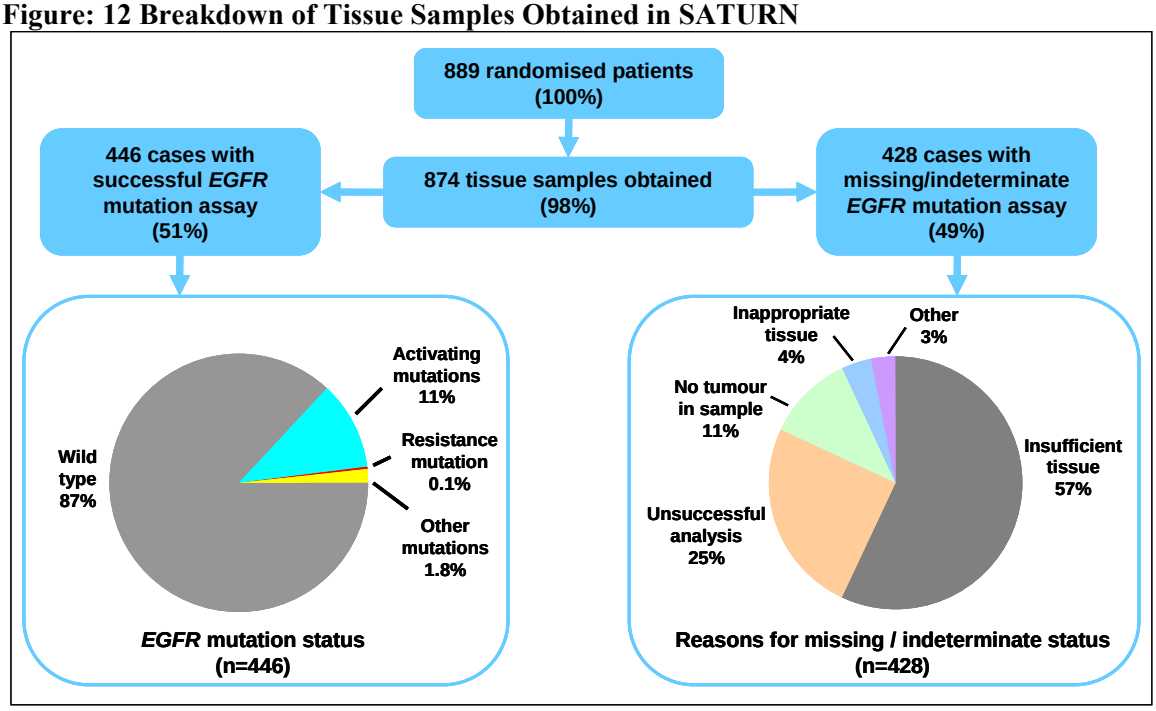


Table 11: Hazard Ratios and 95% Confidence Intervals for PFS by Biomarker Subgroup

		PLACEBO			ERLOTINIB				
Subgroup		Patients per group [N=451]	N Events	Median time	Patients per group [N=438]	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		447	400	11.1	437	349	12.3	0.71	[0.62;0.82]
EGFR IHC Status (new reading)	Positive	311	278	11.1	307	244	12.3	0.69	[0.58;0.82]
	Negative	59	53	9.0	62	48	11.0	0.77	[0.51;1.14]
EGFR FISH (IUO) Status	Positive	110	97	11.6	121	93	16.0	0.68	[0.51;0.90]
	Negative	127	110	11.6	128	102	12.0	0.81	[0.62;1.07]
EGFR Mutation Status	Activating Mutation	22	20	12.6	18	7	59.9	0.09	[0.03;0.25]
	Wild Type	163	143	8.7	165	144	12.0	0.81	[0.64;1.02]
KRAS Mutation Status	Classical Mutation	41	40	6.3	49	43	9.3	0.77	[0.50;1.19]
	Wild Type	198	173	11.4	205	166	12.3	0.70	[0.57;0.87]
	Unknown	207	186	11.3	183	140	13.1	0.70	[0.56;0.87]
EGFR CA-SSR1	Low	195	172	11.1	190	148	12.3	0.68	[0.55;0.85]
	High	203	186	11.4	193	161	12.3	0.75	[0.60;0.92]

PFS [weeks] (TTPFS) - Censoring: PFS Censoring (prim. ana.,1=PD/death) (CSPFS)
Cut-off for statistical analysis: 17MAY2008

Figure 13: Kaplan-Meier Curve of PFS by Study Treatment and EGFR Mutation Status (Activating Mutation and Wild Type)

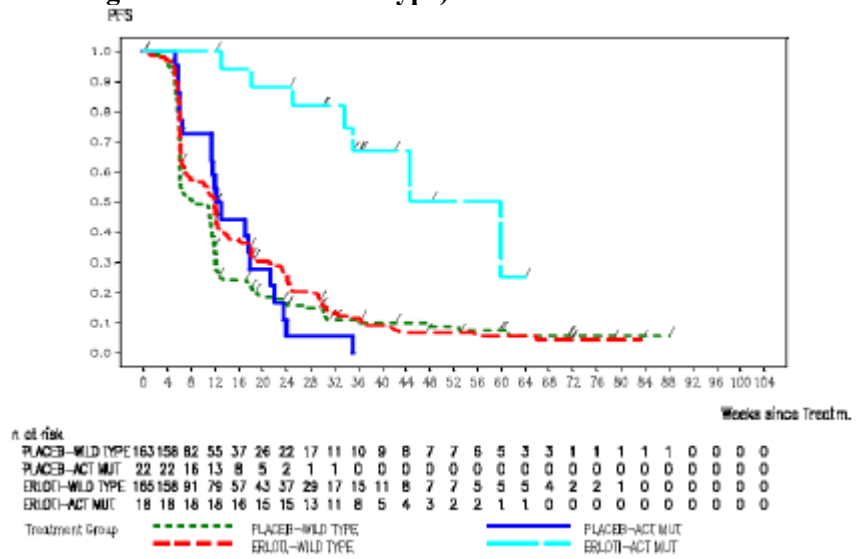
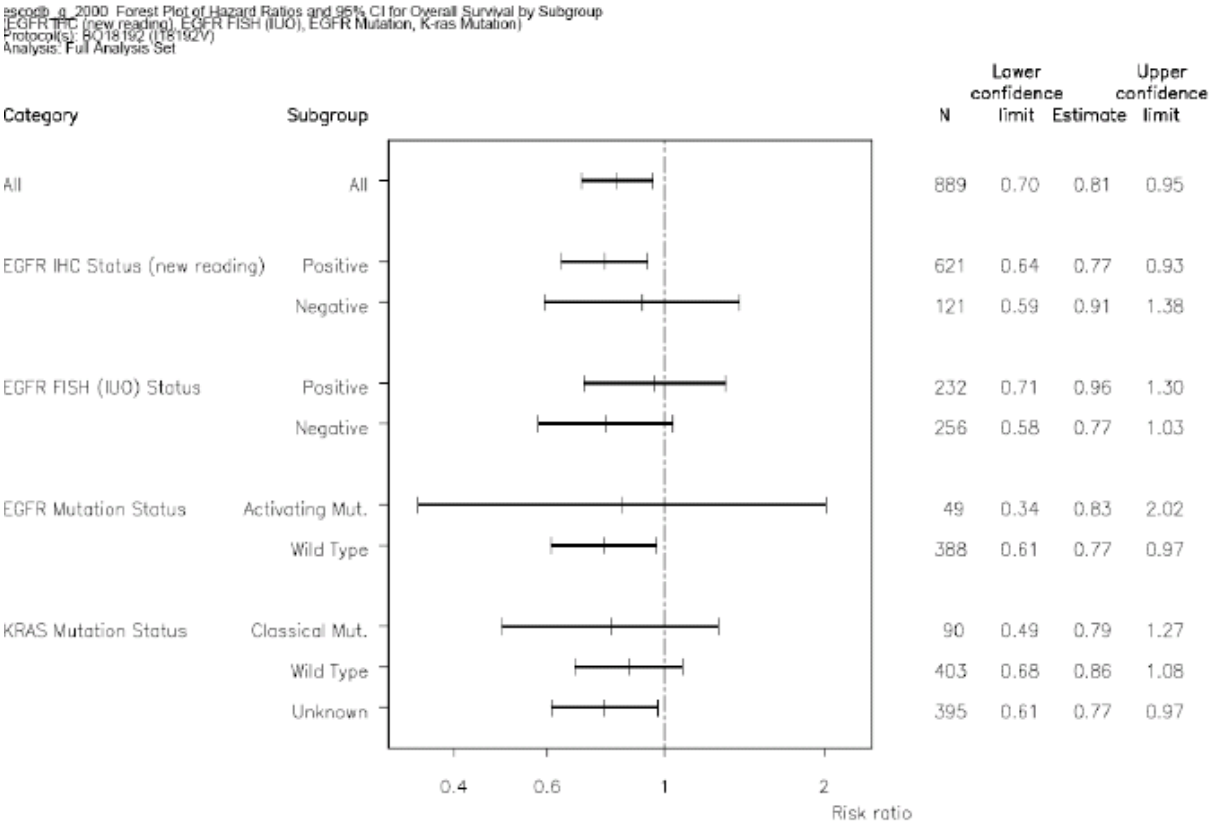


Figure 14: Forest Plot of Hazard Ratios and 95% CI for OS by Biomarker Subgroup



PFS results in erlotinib patients with EGFR mutated tumours show a HR of 0.23 [0.12; 0.45], $p < 0.0001$ (table 12). For the WT subgroup, the results for the PFS show a HR of 0.78 [0.64; 0.96], p=0.0182, table 13).

Table 12: Summary of PFS in the EGFR Mutation Positive Subgroup

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

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

Table 13: Summary of PFS in the EGFR WT Subgroup

	PLACEBO (N=189)		ERLOTINIB (N=199)
Patients with event	179 (94.7 %)		184 (92.5 %)
Patients without event*	10 (5.3 %)		15 (7.5 %)
Time to event (weeks)			
Median#	8.9		12.0
95% CI for Median#	[6.3;11.4]		[10.9;12.7]
25% and 75%-ile	6.0;13.3		6.1;24.1
Range##	0.1 to 119.7		0.1 to 120.3
p-Value (Log-Rank Test)		0.0182	
Hazard Ratio		0.78	
95% CI		[0.64;0.96]	
6 months estimate			
Patients remaining at risk	25		39
Event Free Rate#	0.14		0.21
95% CI for Rate#	[0.09;0.19]		[0.15;0.27]

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

OS data in the EGFR mutation positive subgroup were still immature, particularly in the erlotinib arm, as only 8 patients out of 22 had died by the cut-off date (Table 14). In addition, 67% of placebo patients in the EGFR mutation positive subgroup received second or further line treatment with EGFR-TKIs. The MAH claimed that given the higher sensitivity in this population towards EGFR TKI treatment, this probably explains why the considerable benefit observed in PFS in this population did not translate into an OS benefit.

Table 14: Summary of OS in the EGFR Mutation Positive Subgroup

	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

The summary of overall survival (OS) for EGFR WT patients is given in table 15. Patients with EGFR WT tumours had significantly longer survival with erlotinib treatment compared to placebo as demonstrated by an HR of 0.77 [0.61; 0.97] (p=0.0243).

Table 15: Summary of OS in the EGFR WT Subgroup

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

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

- *Histological subtypes*

A Forest plot showing subgroup analyses for OS by histological type is presented below in Figure 15 and by squamous and non-squamous histology in Figure 16. Patients with squamous cell carcinoma, adenocarcinoma and other histology derived a survival benefit from treatment (HR 0.86, 0.77 and 0.85 respectively), as did patients with non-squamous cell carcinoma (HR 0.79)

Figure 15: Forest Plot of Hazard Ratios and 95% Confidence Intervals for OS by Histological Subgroup

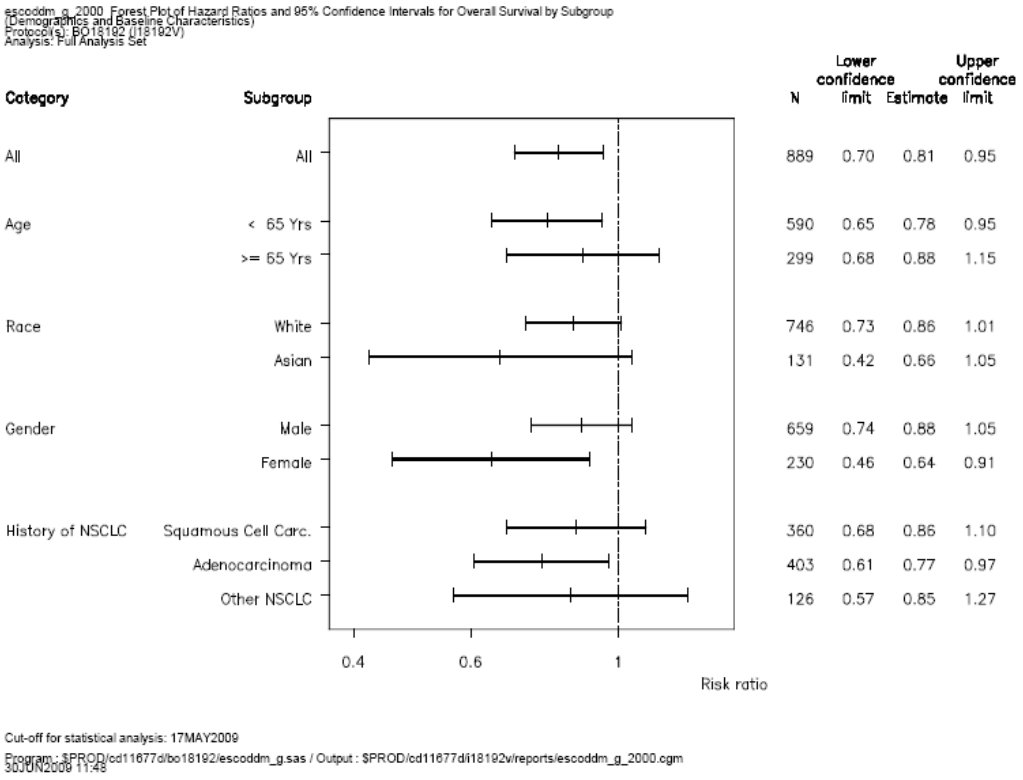
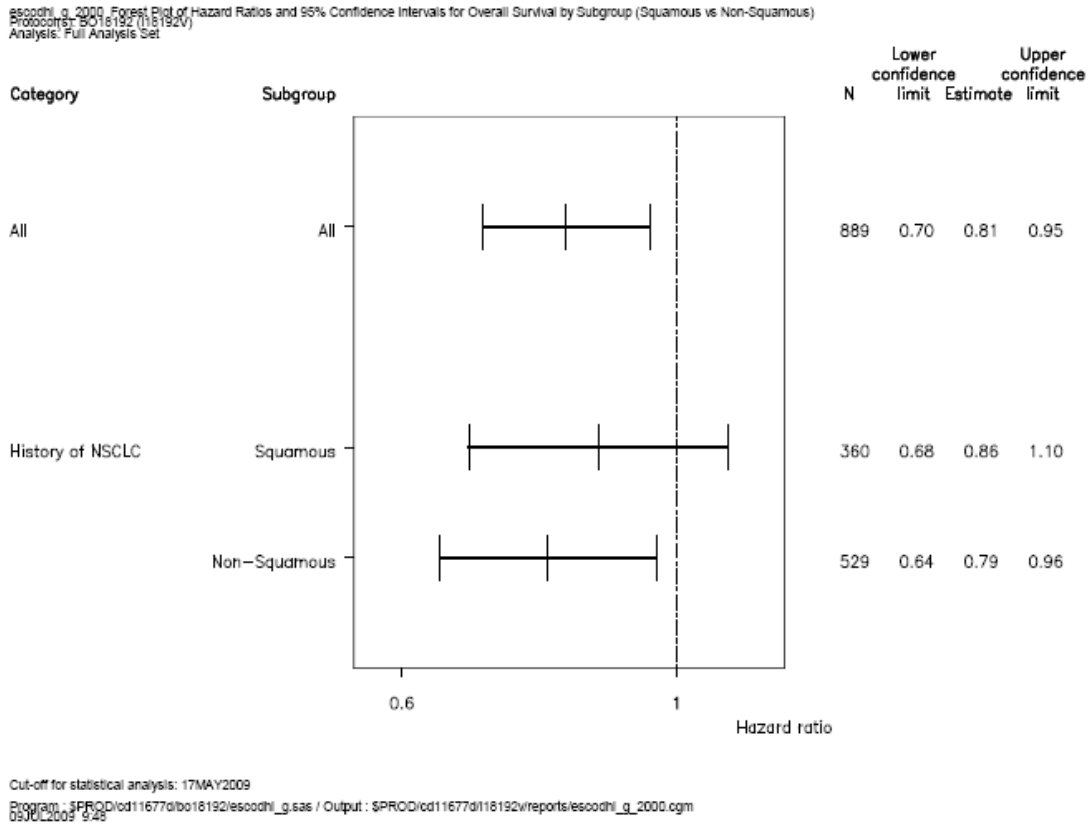


Figure 16: Forest Plot of Hazard Ratios and 95% Confidence Intervals for OS by Histological Subgroup (Squamous and non Squamous)



Kaplan-Meier curves of OS for patients with squamous cell carcinoma, adenocarcinoma and non-squamous carcinoma are given in Figure 17, Figure 18 and Figure 19, respectively.

Figure: 17 Kaplan-Meier Curve of OS for Patients with Squamous Cell Carcinoma

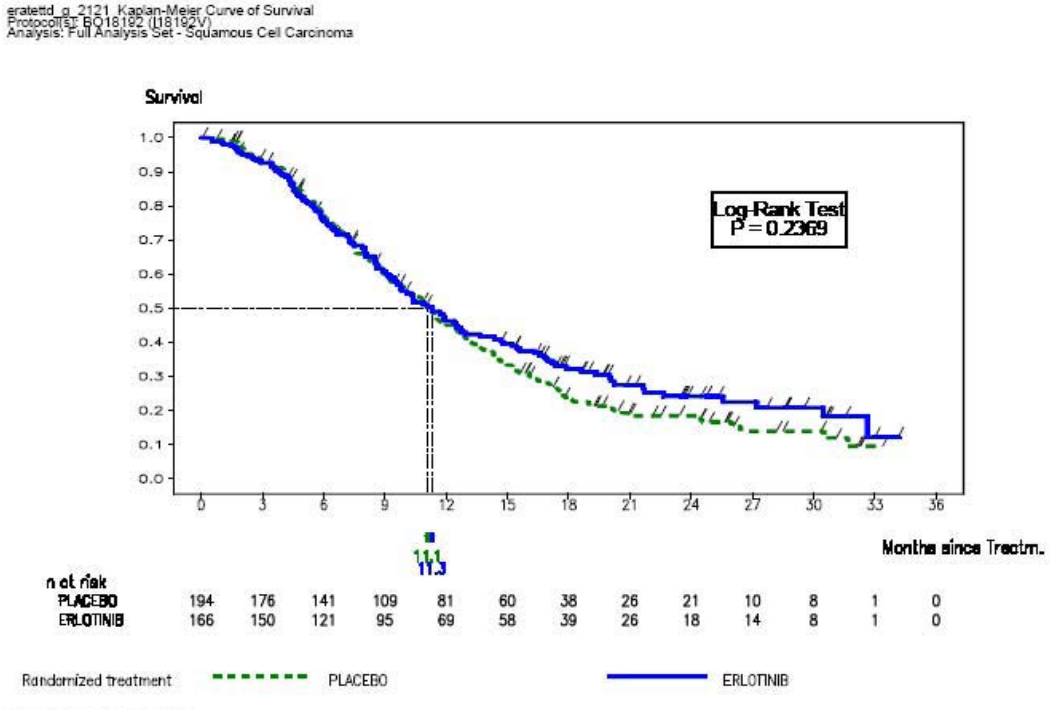


Figure 18: Kaplan-Meier Curve of OS for Patients with Adenocarcinoma

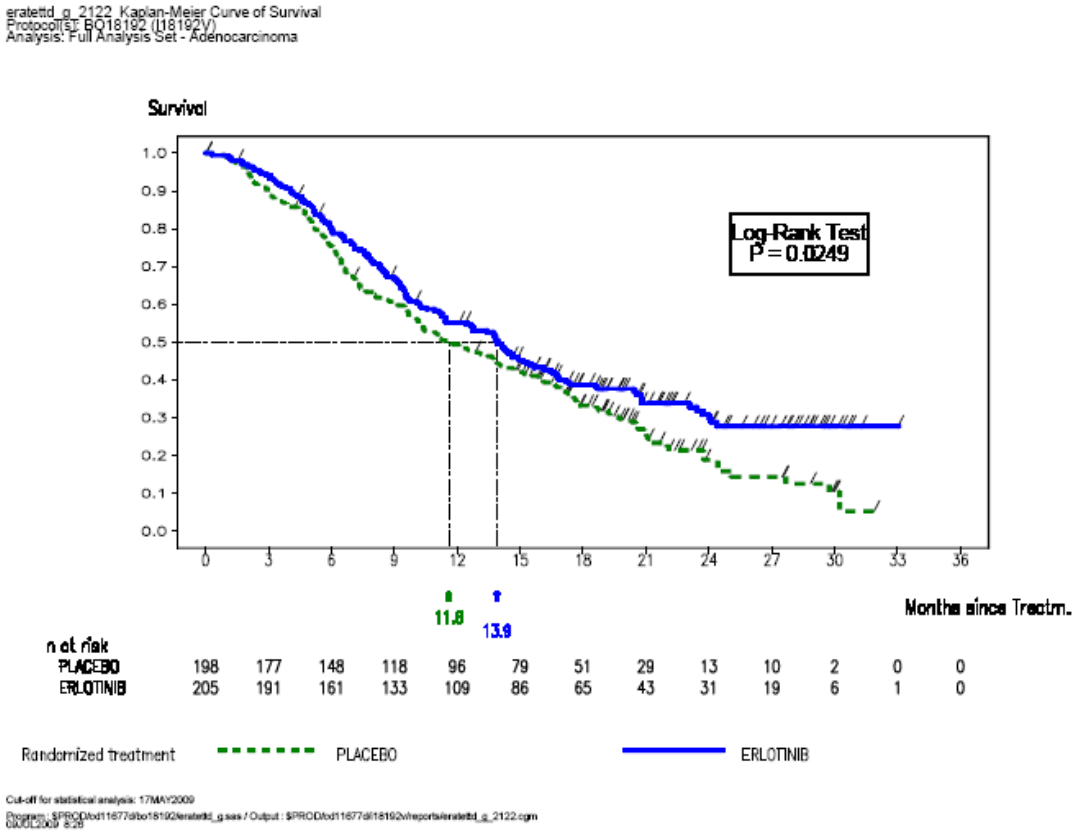
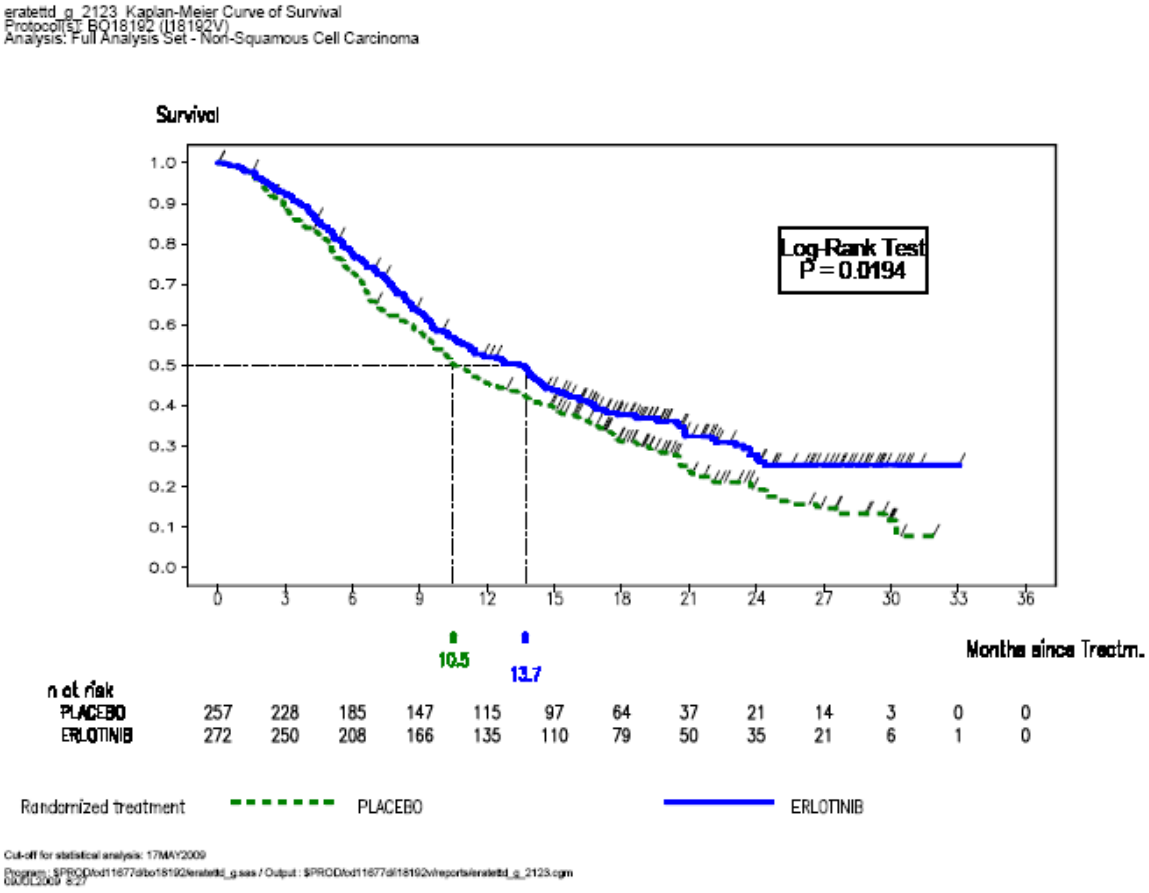
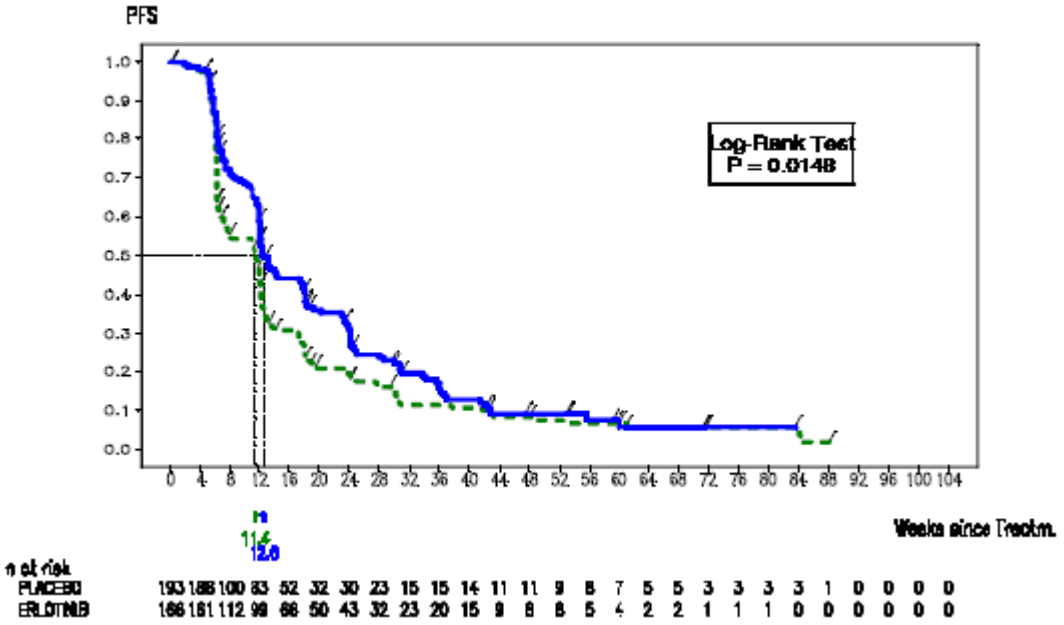


Figure 19: Kaplan-Meier Curve of OS for Patients with Non-Squamous Cell Carcinoma



Kaplan-Meier plots of PFS for patients with squamous cell carcinoma, are given in Figure 20.

Figure 20: Kaplan-Meier curve of PFS for patients with squamous cell histology



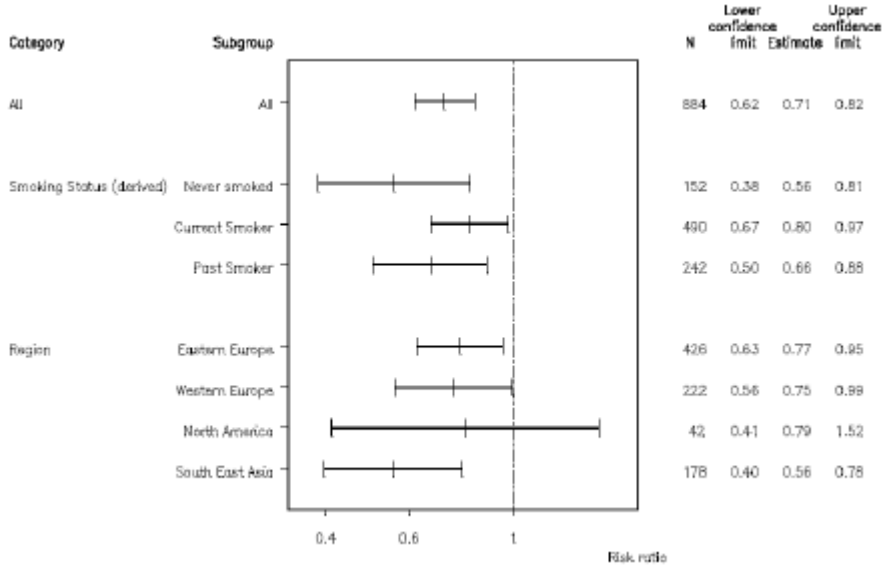
- *Sensitivity and post-hoc analyses*

A series of sensitivity and additional post-hoc analyses have been performed by the MAH to assess the robustness of the PFS results.

1) Association between the investigators and independent review committee determined events of disease progression:
Overall concordance on progression between investigator and central review assessments was 78% for the erlotinib group and 82% for the placebo group. Sensitivity analyses were performed that account for central review determined events of disease progression rather than investigators determined events (for all patients and for patients with EGFR IHC positive population) as well as for tumour assessment at baseline, TTP, Best Overall Response and Response upgrade. Further sensitivity analyses of PFS based on investigator assessment conducted to take into account missing or not-evaluable tumour assessments have been made. According to the MAH the results of the analyses are consistent with the treatment effect observed in the primary analysis of PFS.

2) Subgroup Analyses by Stratification Factors and baseline
According to the MAH, the results were consistent with the treatment effect observed in the primary analysis of PFS.

Figure 21: Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by several Stratification Factors



3) Sensitivity analysis of PFS for FAS population excluding patients who had EGFR activating mutation positive tumours.

According to the MAH the results of this population were similar to those of the overall population (HR 0.76, 95% CI: 0.66, 0.88, p= 0.0002), indicating that the overall PFS result was not entirely driven by the patients with EGFR activating mutation positive tumours.

4) Cox-regression analysis adjusting for individual covariates (stratification factors, demographic and baseline characteristics, histology of NSCLC, previous treatments related to NSCLC, biomarkers).
As stated by the MAH, the HR for the treatment effect was not significantly affected by any of the covariates confirming the robustness of the primary result. Multiple Cox-regressions for PFS adjusted for identified factors (treatment, age, smoking status, disease stage, K-ras mutations and EGFR mutations) showed that the treatment effect was similar to the unadjusted analysis (HR=0.71, p<0.0001). No sign of interaction of K-ras mutation and treatment was observed, but the test for interaction of EGFR mutation and treatment was significant.

In conclusion, for all these sensitivity analyses performed the MAH states that the results are consistent with the treatment effect observed in the primary analysis of PFS.

5) Analysis of NSCLC-related symptomatology
The MAH performed post-hoc analyses of time to pain, cough and dyspnoea. Time to pain and time to analgesics (opioids and other analgesics) were significantly longer for patients receiving erlotinib compared with placebo (HR=0.61, 95% CI: 0.42, 0.88, p=0.008, and HR=0.66, 95% CI: 0.46, 0.94, p=0.0199, respectively).
A not statistically significant trend vs. longer time to cough and time to dyspnoea was also found in the erlotinib group (HR=0.77, 95% CI: 0.49, 1.21, p=0.2546 and 0.75, 95% CI: 0.48, 1.17, p=0.2054, respectively).

6) PFS, OS and EGFR polymorphism by grade of rash
In study BO18192, a trend vs. longer PFS in patients treated with erlotinib who experienced rash of grade ≥ 2 has been reported by the MAH, but the results are not statistically significant. No significant associations between OS and EGFR polymorphism and grade of rash have been found.

CHMP discussion on efficacy data
The CHMP raised one major objection regarding the benefit of erlotinib given as maintenance therapy vs. erlotinib given at progression as currently indicated. OS and PFS benefits of erlotinib when given at progression are of similar magnitude, if not greater, than the ones observed in SATURN study with

erlotinib as maintenance treatment with a gain in median OS of ≥ 2 months and significant improvement in lung related symptoms control (Study BR21).
The MAH justified the use of erlotinib as maintenance therapy instead of 2nd line treatment by explaining that a majority of patients experiences a rapid progression and an irreversible decline in performance status shortly after stopping 1st line therapy. Consequently, a lot of patients miss the opportunity to actually receive a 2nd line therapy. The CHMP however asked the MAH to conduct further analyses to identify which NSCLC patients might benefit from treatment with erlotinib in maintenance setting.

The MAH submitted an updated OS analysis by histological subtype. These results showed that the benefits of erlotinib as maintenance therapy in patients with squamous cell histology are limited to a statistically significant improvement in PFS, but with very modest clinical relevance as a gain in median PFS only less than 1 week was observed. No difference in OS between erlotinib and placebo treated patients has been reported.

In addition, concerns were raised by the CHMP based on the results of the PFS in patients with EGFR IHC negative tumours and preliminary OS analyses showed no statistically significant neither clinically relevant effect of erlotinib in this subgroup of the population.
The MAH commented that the sample size for the subgroup analyses is by definition underpowered and therefore while trends can be assessed in subpopulations, it is not considered justified to expect statistical significance to be shown for all subgroup analyses. The overall study was planned to show a PFS HR benefit of 0.8 as this was considered to be clinically meaningful. As the estimate of the PFS benefit in IHC negative patients (HR of 0.77) was below the pre-defined threshold that had been considered as clinically meaningful, the estimated benefit observed with the IHC negative subpopulation should also be considered as clinically meaningful.
The CHMP didn't agree with the MAH and suggested that at least this subgroup of population should be excluded from any potential indication.

Furthermore, one additional major objection was raised by the CHMP regarding the efficacy of erlotinib in patients without an EGFR activating mutation.
In reply to CHMP concerns, the MAH has provided updated PFS and OS data regarding the subgroup of patients enrolled in SATURN study with known EGFR mutational status.
Based on these data, in the EGFR WT subgroup, the median PFS in placebo-treated patients was 8.9 weeks vs. 12.0 weeks in the erlotinib arm with a HR = 0.78 (95% CI 0.64; 0.96), p=0.0182. The median OS was 10.2 months in the placebo group vs. 11.3 months in the erlotinib group. The HR for OS was 0.77 (95% CI 0.61; 0.97), p= 0.0243.

The Scientific Advisory Group (SAG) -Oncology was consulted on the following questions:

- *Does the SAG consider the use of erlotinib in patients with NSCLC given as maintenance therapy after first-line therapy justified instead of giving it only at progression, as currently indicated, with the advantage of a treatment-free period?*

The SAG discussed the results and design of the available trials and agreed that it was not possible to conclude on the pros and cons of erlotinib given as "maintenance" therapy after first-line therapy *versus* erlotinib given after progression. To address such questions one would most likely need direct comparative data testing the outcome following either of the two strategies, in a relevant population.

Concerning "maintenance" therapy only, the available efficacy data showed only a very modest efficacy in the overall population. A number of exploratory subgroup analyses were presented and larger effects were claimed to be associated with erlotinib treatment in some subgroups. However, the SAG agreed by consensus that these differences were generally of limited clinical and statistical significance (also taking into account the exploratory nature of these analyses), with one notable exception, namely the analysis in the subgroup of patients with tumours with activating mutations in the EGFR gene. In this subgroup, a *dramatic* effect was associated with erlotinib with an estimated HR of .09 (CI: 0.03-0.25). Although some effect was also claimed in patients with EGFR mutation-negative tumours, the SAG agreed that this effect was too marginal to be of any clinical significance.

The SAG agreed by consensus that based on the data presented and knowledge about the role of mutations for tyrosine-kinase inhibitors in NSCLC, presence of activating mutation in the EGFR gene is currently the only convincing characteristic for selecting patients for treatment with erlotinib. It is expected that this characteristic would be necessary regardless of the indication of "maintenance" or second-line.

The SAG did not agree with the argument that some activity was also observed in patients in whom there was no evidence of activating mutation in the EGFR gene, and that this would therefore question the importance of this selection criterion. The SAG argued that the activity in patients in whom there was no evidence of activating mutation was too marginal to be of any clinical significance. Furthermore, the SAG argued that any remaining activity in that subgroup could be due to the low sensitivity of the assay (67%), so that tumours with activating mutation could have wrongly been classified as having no evidence of activating mutation.

The MAH should present a comprehensive analysis of the efficacy and toxicity of erlotinib by presence of activating mutation in the EGFR gene, in the relevant indications, to gain further understanding about the effects in this subgroup.

- *Does the SAG consider the clinical benefit of erlotinib when given as maintenance therapy after first line therapy adequately demonstrated in patients with squamous lung cell tumours where there currently is an unmet medical need, but where only a statistically significant improvement by erlotinib was noted in PFS, but either in OS nor in related symptom control?*

The SAG agreed by consensus that histology was not a good characteristic for selecting patients for treatment with erlotinib. Although small treatment differences were observed in this subgroup depending on erlotinib treatment, due to the exploratory analyses it was difficult to draw firm conclusions. EGFR mutation status appeared to be the only convincing characteristic for selecting patients for treatment with erlotinib (see answer to question No. 1).

- *Does the SAG consider the clinical benefit of erlotinib when given as maintenance therapy after first-line therapy adequately demonstrated in patients with other than predominantly squamous lung cell histology vs. the current standard option, in particular pemetrexed, where the magnitude of benefits in terms of PFS and OS was larger?*

It is difficult to compare the clinical efficacy of erlotinib *versus* other treatment options in the absence of comparative data. The SAG agreed by consensus that histology was not a good characteristic for selecting patients for treatment with erlotinib and that EGFR mutation status appeared to be the only convincing characteristic for selecting patients (see answer to question No. 1).

CHMP conclusion

Further to CHMP request, efficacy in a subgroup of patients with stable disease was analysed by the MAH. In this additional analysis, the HR for PFS was 0.68 (95% CI 0.56; 0.83, p<0.0001) and the HR for OS was 0.72 (95% CI: 0.59; 0.89; p=0.0019). The difference in median OS was 2.3 months. Further exploratory analyses showed that the results were consistent across the levels of other factors, and no imbalances have been identified that could have biased the study results.

The MAH committed 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 MAH and CHMP, to conduct such an investigation. In addition, the MAH committed to provide information to optimize therapy in patients with EGFR activating mutation positive tumours by: 1) a-submission of currently available data and 2) b- Submission of CSR from 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)).

Given the very modest efficacy in the broad indication and the larger treatment effect seen in patients with SD particularly in terms of OS, the CHMP considered that it was necessary to restrict the indication to the subgroups of patients with SD at baseline.

1.2.4 Clinical safety

Patient exposure

The safety population of SATURN study included 433 patients in the erlotinib group and 445 in the placebo group, as 11 patients (5 and 6, respectively) of the FAS were excluded from the safety analysis: seven patients (3 in the erlotinib group, 4 in the placebo group) did not receive study treatment and 4 (2 in each group) did not have any safety follow-up.
The median total cumulative dose of erlotinib was 12,750 mg with median exposure duration of 12.3 weeks. As expected due to the shorter PFS, the placebo group had slightly shorter median duration of exposure (11.7 weeks) and a lower median total cumulative dose (12,300 mg). Ninety-five patients (22%) received study drug for more than 6 months in the erlotinib group compared with 58 patients (13%) in the placebo group.
The median dose intensity in both groups was 150 mg/day.
In the erlotinib group, 11% of patients experienced erlotinib dose reduction to 100 mg daily and 1% had a reduction to less than 100 mg daily. In the placebo group, 3 patients (<1%) had dose reductions. In the erlotinib group 10% of patients had a dose interruption of less than 1 week (placebo group 5%) while 6% had dose interruptions lasting 1 week or more (placebo 1%) (Table 16).

Table 16: Patient Exposure

	Placebo N=442 N. (%)	Erlotinib N=430 N. (%)
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 - Max	750-88500	0-89400
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
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)
Dose Intensity (mg/day)		
Mean	149.3	144.6
SD	4.58	15.23
Median	150.0	150.0
Min - Max	92-154	57-150
Dose Reduction		
No Dose Reduction	439 (99)	381 (89)
Reduction to 100 mg	3 (<1)	47 (11)
Reduction to 50 mg	1 (<1)	4 (<1)
Dose Interruption		
No Dose Interruption	416 (94)	368 (86)
Interruption < 1 week	21 (5)	41 (10)
Interruption ≥ 1 week	6 (1)	26 (6)
Dose Reduction/Interruption	27 (6)	78 (18)

Adverse events (AE)

More patients in the erlotinib group than in the placebo group experienced at least 1 AE (78.8%, compared with 54.2%), AEs leading to withdrawal from treatment (4.6%, compared with 1.6%) or to dose modification or interruption (16.2% vs. 3.4%, respectively) (Table 17). A significantly higher number of patients in the erlotinib group experienced AEs considered related to study treatment (64.9% vs. 20.0%, respectively), severe (Grade ≥ 3) AEs (24.7% vs. 12.1%, respectively), and severe AEs related to study drug (2.3% vs. 0.2%). A large proportion of these differences were due to the higher number of patients who developed rash or diarrhoea in the erlotinib group.

Table 17: Overall Summary of AEs in SATURN Study

	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: According to the CRF study completion page, 19 patients were prematurely withdrawn from the study due to an AE in the erlotinib group. However, 20 patients permanently discontinued the study drug due to an AE in the erlotinib group according to the AE page. [PIRD]

The body systems with the highest incidence of AEs in the erlotinib group were "skin and subcutaneous tissue disorders" (63.0%, vs. 12.6% in placebo group) and "gastrointestinal disorders" (30.5%, vs. 16.0% in placebo group), reflecting the fact that the most common AEs among erlotinib-treated patients were rash and diarrhoea. Other body systems in which there was a higher incidence of AEs on erlotinib treatment include "general disorders and administration site conditions" (23.8% vs. 16.0%, especially due to fatigue, asthenia, pyrexia, mucosal inflammation and xerosis), "infections and infestations" (16.9% vs. 8.1%, primarily due to paronychia, pneumonia and respiratory tract infection), "metabolism and nutritional disorders" (10.4% vs. 7.0%, particularly due to anorexia), "investigations" (7.2% vs. 2.5%), "eye disorders" (4.8% vs. 2.2%, especially conjunctivitis), "psychiatric disorders" (4.6% vs. 2.0%, especially insomnia, anxiety and depression), and "ear and labyrinth disorders" (1.6% vs. 0.2%).

Common AEs

Consistent with findings from other clinical studies of single-agent erlotinib, rash (49.2%) and diarrhoea (20.3%) are the most commonly reported adverse events in the erlotinib group, and were considered by the investigator to be related to study drug in 48.5% and 18.2% of patients, respectively. These were the only AEs with an incidence ≥ 10%.

Adverse events regardless of causality that occurred with an incidence ≥ 3% among erlotinib-treated patients are listed in Table 18. Such AEs have been also considered related to study drug in the majority of patients treated with erlotinib. AEs for which the incidence in the erlotinib arm was notably higher than in the placebo arm include several skin and subcutaneous tissue disorders ([rash 49.2% vs. 5.8%], pruritus [7.4% vs. 2.7%], acne [6.2% vs. 0%], dermatitis acneiform [4.6% vs. 1.1%], dry skin [4.4% vs. <1%]), as well as diarrhoea (20.3% vs. 4.5%), nausea (7.6% vs. 6.1%), fatigue (9.0% vs. 5.8%), asthenia (4.2% vs. 2.9%), pneumonia (3% vs. 1.6%), paronychia (3.9% vs. 0%), anorexia (9.2% vs. 4.9%), and weight decrease (3.9% vs. <1%).

Table 18: Adverse Events Reported in ≥ 3% of Patients in Erlotinib Group (Safety Population SATURN study)

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	-	-

Throughout the SATURN study, most AEs were of mild (grade 1) or moderate (grade 2) severity (grade 1 or 2 events: 54% in the erlotinib group vs. 42% in the placebo group) although there was a higher proportion of patients with ≥ grade 3 adverse events in the erlotinib group (24.7% vs. 12.1%). Among the body systems, ≥ grade 3 adverse events occurred notably more often in the erlotinib group than in the placebo group among skin and subcutaneous tissue disorders (9.0% vs. 0%), gastrointestinal disorders (3.9% vs. <1%), and infections (3.7% vs. 1.6%). These differences were primarily the result of differences in the preferred terms rash (6.0% vs. 0%), diarrhoea (1.8% vs. 0%), and pneumonia (1.8% vs. 0.9%).

Serious adverse events (SAEs) and deaths

Forty-seven patients (10.9%) in the erlotinib group and 34 patients (7.6%) in the placebo group experienced one or more SAEs. Ten patients in the erlotinib group and 1 in the placebo group experienced SAEs that were considered by the investigator as related to study drug. In the erlotinib group, these related serious adverse events were diarrhoea (3 patients), rash (2 patients), interstitial lung disease (ILD) (2 patients), pulmonary fibrosis (1 patient), increased ALT/AST (1 patient) and respiratory tract infection (1 patient). One of the patients with related interstitial lung disease died due to the event. For this patient the cause of death was ultimately assessed as progressive disease, although the investigator could not rule out ILD. The study drug-related SAEs reported in SATURN study are consistent with the know safety profile of single-agent erlotinib.
Other SAEs regardless of causality that occurred in more than 1 patient in the erlotinib group were pneumonia (erlotinib 7 patients, placebo 4 patients), diarrhoea (erlotinib 4 patients, placebo none), dyspnoea (2 patients in each group), and cardio-respiratory arrest (erlotinib 2 patients, placebo none).

Study BO18192 is ongoing, with follow-up continuing for patients alive at the time of the study cut-off date (17 May 2008) to provide data for a final analysis of overall survival. At the time of the study cut-off, 157 patients in the erlotinib group and 176 patients in the placebo group had died during the follow-up phase, most due to disease progression (148 and 171 patients, respectively).
Sixty-six patients died during the treatment phase (or within 28 days of last dose), 35 patients in the erlotinib group (8.1%) and 31 patients in the placebo group (7.0%): of them, 26 and 27 patients, respectively, died due to progressive disease. Nine patients in the erlotinib group and 3 patients in the placebo group died on-study due to an AE. None of these events have been assessed as causally related to erlotinib (Table 19).
An additional 3 patients (1 in the erlotinib group [Interstitial lung disease] and 2 in the placebo group [haemoptysis, cerebrovascular accident]) had Grade 5 AEs, but the final investigator assessment was that they died due to disease progression. However, in the investigator's opinion, the event of interstitial lung disease was related to erlotinib.

Table 19: Summary of Deaths During Treatment Phase

	Placebo N = 445	Erlotinib N = 433
Total Number of Deaths	31 (7.0%)	35 (8.1%)
Progressive Disease	27 (6.1%)	26* (6.0%)
Adverse Event	4 (0.9%)	9 (2.1%)
Preferred Term:	Cardiac Tamponade Empyema Dyspnea Pulmonary Embolism**	Cardio-respiratory Arrest (2 patients) Pneumonia Sudden Death Drowning Respiratory Failure Cardiac Failure Dehydration Iliac Artery Thrombosis

* One of these patients had grade 5 AE of ILD considered related to study drug.
**No SAE form was received for this patient

Adverse Events leading to withdrawal

Twenty patients (4.6%) in the erlotinib group and 7 patients (1.6%) in the placebo group discontinued study medication as a result of an AE. Among these 20 patients, 12 had AEs considered related to study drug. Five patients in the erlotinib group were withdrawn due to rash (all considered related to study drug) and 2 due to diarrhoea (both considered related to study drug). Other AEs leading to withdrawal in the erlotinib group included interstitial lung disease (2 patients), cardiorespiratory arrest, dermatitis acneiform, gastric perforation, pneumonia, non-cardiac chest pain, pulmonary fibrosis, fatigue, urogenital haemorrhage, cardiac failure, dyspnoea, and transaminases increased.

In the erlotinib group, 36 patients (8.3%) had dose modifications (interruptions or reductions) due to rash (none in the placebo group), and 14 patients (3.2%) had dose modifications due to diarrhoea (1 in the placebo group).

Laboratory findings

In general, the abnormalities in clinical laboratory data reported in SATURN study are consistent with laboratory evaluation results observed in previous clinical studies performed with erlotinib.

Blood Chemistry: Grade 1 or 2 laboratory parameter values were common in both treatment groups. There were no grade 4 AST, ALT, bilirubin, or alkaline phosphatase values recorded during the study among patients who received erlotinib. There were 10 occurrences of grade 3 liver function test increases in 8 patients. Two patients in the erlotinib group with normal AST and ALT values at baseline experienced grade 3 AST and ALT values during the study (1 with an AE reported as transaminase increase) and 3 additional patients with normal ALT values at baseline experienced grade 3 ALT values during the study (all of whom had ALT increases reported as AEs). None of these 5 patients had known liver metastasis. Grade 3 elevations in alkaline phosphatase occurred in 2

patients (neither with associated reported AE), one with a grade 1 value at baseline (no reported metastasis) and one with a grade 2 value at baseline (reported liver metastasis).
One patient in the erlotinib group with a normal total bilirubin at baseline developed a grade 3 bilirubin value during the study, which was also reported as a grade 3 adverse event.
In the erlotinib group, grade 4 blood chemistry laboratory parameter values were limited to 2 patients with normal potassium levels at baseline who had grade 4 elevations during the study (neither of whom had diarrhoea reported as an adverse event) and 1 patient with grade 4 decline in potassium who was receiving 2 diuretics during the study. One patient in the erlotinib group had a grade 3 creatinine value during treatment, after entering the study with grade 1 creatinine at baseline. This increase on Day 130 was reported as acute renal failure on the AE CRF. The patient was treated with intravenous fluids and the condition resolved without sequelae. The acute renal failure was considered by the investigator to be not related to erlotinib.
Haematology: The erlotinib group had more patients shift from normal white blood cell count at baseline to grade 1 during the study compared to the placebo group (15 patients vs. 9 patients) and for lymphocytes (21 patients vs. 8). Grade 3 and 4 haematology laboratory parameter values were uncommon and not associated with clinically significant events.

Safety in patients with stable disease (SD)

The frequency and intensity of AEs observed for the SD population is in line with the AE results observed in the overall population (Table 20). More patients in the erlotinib group than in the placebo group experienced at least one AE. However, the majority of AEs reported were mild or moderate in intensity (NCI-CTC Grade 1 or 2). Similar to the overall population, the most commonly reported AEs in the SD population for patients receiving erlotinib were "rash" (overall: 60.3% erlotinib versus 9.4% placebo; SD: 61.2% erlotinib versus 9.9% placebo) and diarrhoea (overall: 20.3% erlotinib versus 4.5% placebo; SD: 21.2% erlotinib versus 4.7% placebo).

Overall, the incidence of AEs leading to withdrawal was low in both the SD and overall populations (table 20). In the SD population only 9 patients (3.6%) in the erlotinib arm had an AE leading to withdrawal considered to be related to study treatment compared to 1 patient in the placebo group.

Table 20: Overview of Adverse Events, Withdrawals, and Deaths During the Treatment Phase – SD and Overall Safety Population

	SD Population		Overall Population	
	Placebo N=233 No. (%)	Erlotinib N=250 No. (%)	Placebo N=445 No. (%)	Erlotinib N=433 No. (%)
Total patients with at least one AE	134 (57.5)	196 (78.4)	241 (54.2)	341 (78.8)
Total number of AEs	389	756	700	1268
Deaths#	22 (9.4)	23 (9.2)	31 (7.0)	35 (8.1)
Study withdrawal due to an AE#	5 (2.1)	15 (6.0)	7 (1.6)	19 (4.4)
Patients with at last one				
AE leading to death	5 (2.1)	7 (2.8)	5 (1.1)	10 (2.3)
Serious AE	23 (9.9)	33 (13.2)	34 (7.6)	47 (10.9)
Related serious AE	0	5 (2.0)	1 (0.2)	10 (2.3)
AE leading to withdrawal from treatment	5 (2.1)	16 (6.4)	7 (1.6)	20 (4.6)
AE leading to dose modification/interruption	8 (3.4)	40 (16.0)	15 (3.4)	70 (16.2)
Related AE	47 (20.2)	165 (66.0)	89 (20.0)	281 (64.9)
Related AE leading to withdrawal from treatment	1 (0.4)	9 (3.6)	2 (0.4)	12 (2.8)
Severe AE	37 (15.9)	64 (25.6)	54 (12.1)	107 (27.7)

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.

Deaths

A summary of deaths that occurred during the treatment phase of the study is provided in Table 21 for both the overall and SD populations. The incidence of deaths is comparable for both populations.

In the SD population, 45 patients died during the treatment phase, 23 patients in the erlotinib group (9%) and 22 patients in the placebo group (9%). Seven patients in the erlotinib group and 5 patients in the placebo group had Grade 5 AEs. All Grade 5 AEs in both treatment groups were considered unrelated to study treatment.

Table 21: Summary of Deaths During the Treatment Phase – SD and Overall Safety Population

	SD Population		Overall Population	
	Placebo N=233 No. (%)	Erlotinib N=250 No. (%)	Placebo N=445 No. (%)	Erlotinib N=433 No. (%)
Total No. of Deaths	22 (9.4%)	23 (9.2%)	31 (7.0%)	35 (8.1%)
Progressive Disease	19 (8%)	16 (6%)	27 (6%)	26 (6%)
Adverse Event	3 (1)	7 (3)	3 (<1%)	9 (2%)

Extent of Exposure, Dose Modifications and Interruptions

The dose intensity was comparable in both the SD and the overall populations. In the SD population, the median dose intensity in both erlotinib and placebo arms was 150 mg/day, ranging from 59 mg to 150 mg in the erlotinib group and 106 mg to 150 mg in the placebo group. Overall, the proportion of patients needing dose reductions or interruptions was low in the SD population and was comparable to the overall population.

Among patients who received erlotinib, 26 (10%) had their dose reduced from 150 mg to 100 mg and 3 (1%) had further dose reductions. Erlotinib dose interruptions lasting less than 1 week occurred in 6% of the patients, while 10% had dose interruptions lasting > 1 week. Overall, 46 patients (20%) in the erlotinib group had a dose reduction or interruption. Only 1 patient in the placebo group had dose reductions and 14 patients (6%) had dose reductions or interruptions.

Safety in special groups

The incidence of adverse events regardless of causality occurring in at least 5% of the patients was analyzed by gender, age (< 65 vs. ≥ 65 years), race (White vs. Asian), and baseline performance status (0 vs. 1). In general, the observations from analyses of intrinsic factors are as expected and consistent with those reported for similar analyses performed in other erlotinib studies. Specifically, overall adverse event incidences are higher among women compared with men, older patients compared with younger patients, and ECOG PS 1 patients compared with ECOG PS 0 patients. No association was found between incidence of adverse events and smoking status. In addition, consistent with previous analyses was the observation that Asians had a notably higher incidence of adverse events when compared with Whites: Asians receiving erlotinib reported a significantly higher incidence of skin disorders (90.2% vs. 57.9%, especially rash [74% vs. 45%]), gastrointestinal disorders (44.3% vs. 27.6%, mostly diarrhoea [31% vs. 18%], nausea [11.5% vs. 7.1%], and anorexia [14.8% vs. 8.5%]), respiratory and thoracic events (50.8% vs. 16.9%), general disorders and administration site conditions (37.7% vs. 20.8%), infections and infestation (42.6% vs. 12.6%), nervous system disorders (18.0% vs. 9.8%), musculoskeletal and connective tissue disorders (16.4% vs. 9.0%), and metabolism and nutrition disorders (16.4% vs. 9.6%).

Risk Management Plan

The MAH has provided a Risk Management Plan (RMP) version 1.1 which included a risk minimisation plan, with the application for the extension of indication.

Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Identified Risks		
Cutaneous toxicity	Routine pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: 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 section 4.8). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. SmPC Section 4.8. Undesirable effects: In general, rash 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 sun screen (e.g. mineral-containing) may be advisable Skin and subcutaneous tissue disorders: Common: Alopecia. Common (in PA.3): Dry skin. Common: Paronychia. Uncommon Hirsutism, eyebrow changes and brittle and loose nails. Uncommon Mild skin reactions such as hyperpigmentation. Very rare: Cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal.
ILD	Routine pharmacovigilance Guided questionnaire	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Cases of ILD have been reported. Confounding factors (prior chemotherapy and radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, pulmonary infections) were frequent. If ILD is diagnosed, Tarceva treatment should be discontinued. SmPC Section 4.8. Undesirable effects: serious interstitial lung disease
Liver Injury	Routine pharmacovigilance Guided questionnaire	Routine risk minimisation by means of labelling SmPC Section 4.4: Special warnings and precautions for use. Rare cases of hepatic failure have been reported. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Periodic liver function testing should be considered. Tarceva dosing should be interrupted if changes in liver function tests are severe.

		SmPC Section 4.8. Undesirable effects: increased ALT, AST and bilirubin; hepatic failure
GI fluid loss	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: In the event of severe or persistent diarrhoea, nausea, anorexia or vomiting associated with dehydration, Tarceva therapy should be interrupted and appropriate measures taken to treat the dehydration. SmPC Section 4.8. Undesirable effects: diarrhoea, nausea, vomiting, abdominal pain, dyspepsia, flatulence
GI Perforation	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease is at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation SmPC Section 4.8. Undesirable effects: Uncommon: Gastrointestinal perforations.
Ocular toxicities	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: 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. SmPC Section 4.8. Undesirable effects : Eye disorders: Common: Keratitis. Common: Conjunctivitis in study PA.3. Uncommon: Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes). Very rare: Corneal ulcerations and perforations.
Interaction with coumarin anticoagulants	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with other medicinal products: Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR. SmPC Section 4.8. Undesirable effects. Some cases of gastro-intestinal bleeding have been associated with concomitant warfarin administration.

Potential Risks		
Thrombotic Microangiopathy	Routine pharmacovigilance Guided questionnaire	Risk minimization measures not proposed
Missing Information		
Pregnancy and lactating	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.6. Pregnancy and lactation. SmPC Section 5.3. Preclinical safety data.
Paediatrics	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.2 Posology and method of administration.
Cardiac disorders	Routine Pharmacovigilance	Risk minimization measures not proposed
Interaction with ketoconazole	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with other medicinal products: caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.
Interaction with ciprofloxacin	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with other medicinal products: Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced

The Annex II has been updated accordingly.
The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.
The RMP was acceptable to the CHMP.

Discussion on clinical safety

The safety profile of erlotinib as observed in SATURN study (B018192) appears to be consistent with that observed in previous clinical studies of single-agent erlotinib in NSCLC and during post-marketing surveillance. Patients receiving erlotinib in SATURN study experienced diarrhoea (all grades [20.3%] and grade ≥ 3 [1.8%]) and rash (all grades [49%]) at significantly lower incidence than observed in other study conducted in NSCLC (i.e., BR 21, 55%, 6% and 76%, respectively) where erlotinib was administered as monotherapy at the same starting dose. Differences in study populations could eventually explain these discrepancies, as lower incidence of the same adverse events were reported also in the placebo group of SATURN study compared with placebo group of BR21 study (rash all grades: 5.8% vs. 17%; diarrhoea all grades: 4.5% vs. 19%, respectively).
The safety profile of erlotinib as observed in Study BO18192 is consistent with that observed in previous clinical studies of single-agent erlotinib in NSCLC and during post-marketing surveillance. No new unexpected safety signals have been observed.

Overall Discussion and Benefit-Risk assessment

In the full analysis set, erlotinib was associated with a statistically significant improvement in the primary endpoint PFS (HR=0.71, 95% CI: 0.62, 0.82, p<0.001).

Concerning secondary efficacy endpoints, erlotinib was also associated with an improvement in OS (HR: 0.81, 95% CI: 0.70, 0.95; p= 0.0088), however no improvement in quality of life or cancer related symptom control was reported.

In line with the advice of the SAG-Oncology, the CHMP concluded that the benefit in terms of PFS and OS was considered marginal and, as it was not supported by an improvement in quality of life or cancer related symptom control, and did not outweigh the risks associated with treatment. The evaluation of the adverse events experienced by patients confirmed that patients treated with erlotinib presented a statistically significant higher incidence (compared with placebo) of adverse events, serious adverse events and adverse events leading to withdrawal, with diarrhoea, rash and infections being the most frequent side effects reported in a significant part of the population. Thus, the CHMP requested the applicant to try to identify a restricted population for whom the benefit-risk balance could be considered favourable with a clinically relevant effect in terms of important clinical efficacy endpoints.
Following the SAG recommendations the CHMP assessed the subgroup of patients with EGFR activating mutations. In this subgroup the effect in terms of PFS associated with erlotinib administration (HR 0.23, 95% CI 0.12, 0.45, p<0.0001, median PFS 13.0 weeks with placebo versus 46.1 weeks with erlotinib) was very large. However, this analysis was based on too few patients to draw any firm conclusion.
In a subgroup of patients with stable disease it was observed based on post hoc analysis that the treatment effect was larger (HR for PFS 0.68, 95% CI 0.56; 0.83, p<0.0001 and HR for OS 0.72, 95% CI: 0.59; 0.89; p=0.0019). Albeit based on post-hoc analyses of a secondary endpoint, the effect observed in the subgroup of patients with SD at baseline was considered of clinical relevance in this patient population with a generally poor prognosis. The treatment effect was consistent across strata and endpoints, and no important imbalances have been identified that could have biased the study results. In addition, the frequency and intensity of AEs observed for the SD population was in line with the AE results observed in the overall population.

Therefore, the CHMP considered that the Benefit-Risk ratio of erlotinib for the restricted indication as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease following 4 cycles of standard platinum-based first-line chemotherapy is positive.

All the proposed consequential changes to sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC and the Package Leaflet were agreed.

Further, the MAH has updated annex II to reflect the latest version of the Risk Management Plan (version 1.1) agreed with the CHMP.

II. CONCLUSION

On 18 March 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.