17 December 2015
EMA/CHMP/816728/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tarceva

International non-proprietary name: erlotinib

Procedure No. EMEA/H/C/000618/II/0043

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
AI	accuracy interval
ATP	adenosine triphosphate
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response (RECIST Criteria)
CSR	clinical study report
DCR	disease control rate
ECOG PS	Eastern Cooperative Oncology Performance Status
EGFR	epidermal growth factor receptor (HER 1)
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HR	hazard ratio
IHC	immunohistochemistry
ILD	interstitial lung disease
ITT	intent to treat
MAH	Marketing authorisation holder
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PR	partial response (RECIST criteria)
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse events
SD	stable disease
SOC	system organ class
TKI	tyrosine kinase inhibitors
TTP	time to progression

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 6 October 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Modification of the indication to limit maintenance treatment to NSCLC patients with an EGFR-activating mutation based on the data from study BO25460 (IUNO). Consequently, SmPC sections 4.1, 4.8 and 5.1 have been updated. The Package leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

EMA Decision CW/0001/2015 on the granting of a class waiver includes the condition related to the modified indication of Tarceva.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	6 October 2015
Start of procedure:	19 October 2015
CHMP Rapporteur Assessment Report	24 November 2015

Timetable	Actual dates
CHMP members comments	7 December 2015
Updated CHMP Rapporteur Assessment Report	11 December 2015
Opinion	17 December 2015

2. Scientific discussion

2.1. Introduction

Erlotinib is an EGFR TKI that was developed for the treatment of NSCLC, pancreatic cancer, and other solid tumors. Erlotinib exerts its therapeutic activity through direct and reversible inhibition of the EGFR tyrosine kinase. Erlotinib was approved in the EU on 19 September 2005. Erlotinib is currently approved in the EU for the following indications:

- First-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.
- Monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy.
- Treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.
- In combination with gemcitabine for the treatment of patients with metastatic pancreatic cancer.

In order to provide support for first-line maintenance treatment with erlotinib in NSCLC patients whose tumors harbor EGFR activating mutations, results are provided from a pre-specified subpopulation analysis of Study BO18192 (SATURN), a multi-center, randomized, double-blind, placebo controlled Phase 3 study of single-agent erlotinib in patients with Stage IIIb/IV NSCLC who had not progressed following 4 cycles of platinum-based chemotherapy. Patients in this study were randomized to treatment with erlotinib (150 mg/day) or placebo until disease progression, death or intolerable toxicity. This subpopulation analysis evaluated treatment response to erlotinib versus placebo in NSCLC patients with tumors harboring EGFR-activating mutations (exon 19 deletions or exon 21 L858R mutations). The efficacy data in this subpopulation of 22 erlotinib-treated patients were previously submitted to the Committee for Medicinal Products for Human Use (CHMP) as part of the Responses to Questions for Type II Variation EMEA/H/C/618/II/017.

At the time of approval of the first-line maintenance indication in the United States, the Food and Drug Administration (FDA) requested a postmarketing commitment to conduct a randomized controlled study in patients with histologically documented, advanced, or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC who have not experienced disease progression or unacceptable toxicity during chemotherapy with four cycles of platinum-based chemotherapy. The study BO25460 (IUNO) was to compare erlotinib as first-line maintenance therapy with erlotinib at progression (second-line treatment); all eligible patients were to have known EGFR by immunohistochemistry (IHC) status and were to be without EGFR activating mutations. Patients with EGFR activating mutations were excluded as it was considered unethical to have such patients potentially being randomized to placebo in the first-line maintenance setting.

The purpose of this Type II variation is to modify the approved indication associated with the first-line maintenance treatment of NSCLC. The proposed changes to the indication were as follows:

'Tarceva is indicated for the first-line and maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations.'

~~'Tarceva is also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.'~~

Preliminary results from study BO25469 (IUNO) and the final CSR from study BO18192 (SATURN) are provided in order to support the above change in the indication. The SATURN study has previously been assessed by the CHMP (EMA/CHMP/298837/2010) and was the basis for the use of erlotinib in the maintenance setting. Furthermore, three published scientific paper[1,2,3] are also provided as supporting literature.

The final indication was as follows:

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

Tarceva is indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy. ~~Tarceva is also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.~~

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Table 1. Tabular overview of clinical studies

Study No. (Phase)	Study Population	Design	No. of Patients	Dose, Route, and Regimen
BO25460 (IUNO)	Previously treated patients with stage IIIB/IV NSCLC who had not progressed after completing 4 cycles of chemotherapy. Patients with EGFR activating mutations were excluded.	MC, R, PC, 2-arm, Ph 3	322 early erlotinib 321 late erlotinib	Early Erlotinib (first-line maintenance) 150 mg erlotinib daily p.o. maintenance treatment until PD, death or unacceptable toxicity. If amenable, open-label second-line treatment with an approved chemotherapy or best supportive care. Late Erlotinib (second-line therapy) Placebo until PD, death or unacceptable toxicity. If amenable, open-label second-line with 150 mg erlotinib daily p.o until PD, death or unacceptable toxicity
BO18192 (SATURN) [1033732]	Previously treated patients with stage IIIB/IV NSCLC who had not progressed after completing 4 cycles of chemotherapy.	MC, R, DB, PC, Ph 3	22 erlotinib 27 placebo Patients with EGFR activating mutations	First-line maintenance 150 mg erlotinib daily p.o. until PD, death or unacceptable toxicity

MC, multicenter; R, randomized; DB, double-blind; PC, placebo-controlled; EGFR, epidermal growth factor receptor; p.o., oral; PD, progressive disease; NSCLC, non-small-cell lung cancer.

2.4. Clinical efficacy

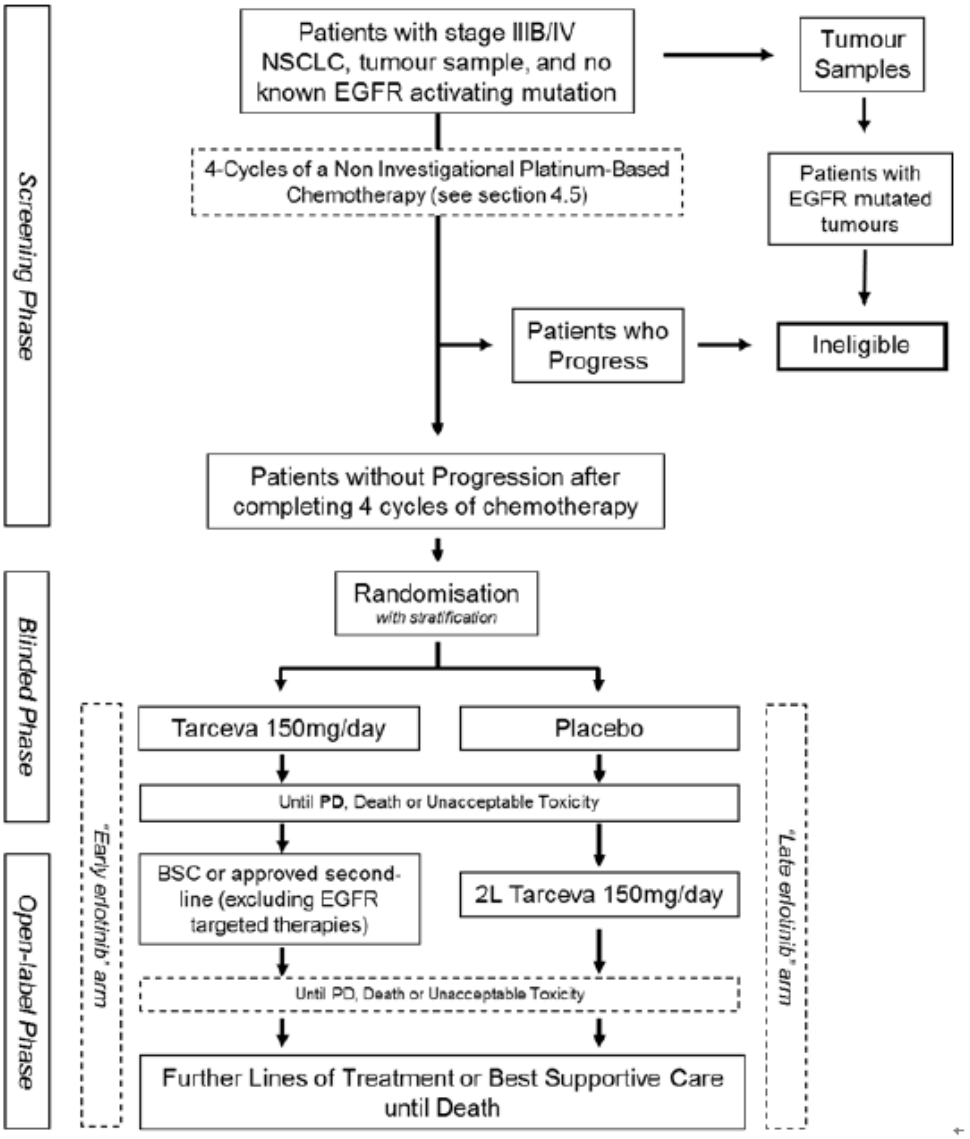
2.4.1. Main studies

IUNO study: A multicenter, multinational, randomized, placebo-controlled,2-arm Phase III study designed to evaluate the relative survival benefit and safety of 'early' (first-line maintenance) erlotinib versus 'late' (second-line) erlotinib in patients with advanced (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC whose tumours did not harbour an EGFR-activating mutation and who had not progressed following 4 cycles of platinum-based chemotherapy.

Methods

A descriptive representation is presented in Figure 1.

Figure 1: BO25460 (IUNO) study design



Study participants and treatments

Patients were initially screened into a chemotherapy run-in period in which they had to complete 4 cycles of an approved (non-investigational) platinum-based doublet chemotherapy without subsequent disease progression (i.e., had documented complete response/partial response or stable disease according to Response Evaluation Criteria in Solid Tumours [RECIST] v1.1 criteria) for eligibility.

- **Blinded phase**: patients whose tumours were confirmed to lack an EGFR activating mutation (exon 19 deletion or exon 2 L858R mutation) or had an indeterminate EGFR mutation status following central testing were randomized to receive 150 mg/day erlotinib ('early erlotinib' group) or placebo ('late erlotinib' group) in the maintenance setting until the occurrence of disease progression (according to RECIST v1.1 criteria or because of symptomatic deterioration attributed to suspected tumor progression), death, or unacceptable toxicity.

- **Open-label phase**: following randomization, patients who had disease progression in the blinded phase were unblinded and entered the open-label phase of the study. Patients randomized to the 'early erlotinib' group received approved second-line (excluding EGFR-targeted) therapies, whereas patients in the 'late erlotinib' group received 150 mg/day erlotinib. Patients were monitored until the occurrence of disease

progression (assessed according to radiological or symptomatic deterioration criteria per local practice), death, or unacceptable toxicity. Patients unable to receive second-line open-label treatment received best supportive care (BSC) until such time they could receive it, or alternatively proceeded directly to Survival Follow-up.

Patients who had documented disease progression at the end of second-line treatment in the open-label phase, or who were not amenable to second-line openlabel treatment at the end of the blinded phase, entered survival follow-up in which they could receive further lines of cancer therapy or BSC at the discretion of the investigator. Survival status was monitored.

Objectives

The primary objective of the study was:

- To compare the overall survival (OS) of first-line maintenance therapy with erlotinib ('early erlotinib') versus erlotinib administered at the time of disease progression ('late erlotinib').

Secondary objectives of the study were:

- To compare progression-free survival (PFS) between the 'early erlotinib' (erlotinib) and 'late erlotinib' (placebo) groups during the blinded (first-line maintenance) phase.

- To compare overall response rate (ORR) and disease control rate (DCR) between treatment groups during the blinded (maintenance) phase

- To evaluate the safety and tolerability profile of erlotinib in this patient population

Outcomes/endpoints

The primary efficacy parameter of overall survival was defined as the time from the date of randomization to the date of death, regardless of the cause of death.

Disease progression in the blinded phase was defined according to RECIST version v1.1. Duration of PFS was assessed during the blinded phase of the study, defined as the time from randomization to disease progression or death, whichever occurred first.

Blinding (masking)

The first phase of the study was double-blinded and the second phase of the study was open-label.

Statistical methods

The primary endpoint of OS was assessed using a 2-sided unstratified log-rank test at a 5% significance level. Median survival time and 95% confidence limits were estimated using Kaplan-Meier (KM) methodology. One-year survival rates from randomization were compared using estimates from the KM survival curves. Estimates of treatment effect were expressed as hazard ratios (HR) ('early erlotinib' group versus 'late erlotinib' group) with 95% confidence intervals (CIs).

The analysis was planned to be performed when 460 death events had been recorded, and has now been conducted. As per protocol, the study ends when the final analysis for the primary endpoint has been performed. The final results became available on 30 July 2015 and the final analysis for the primary endpoint has been performed. Therefore, the study will now be closed.

Results

Participant flow

A total of 643 patients were enrolled and randomized between September 2011 and June 2014. The date of data cut-off for the primary analysis was 23 March 2015, at which time there were 477 death events recorded (74% of randomized patients). The date of the snapshot for the analysis of this ongoing study was 10 July 2015. Of the 643 patients, 322 patients were randomized to receive 150 mg/day erlotinib ['early erlotinib' group] and 321 patients were randomized to receive placebo ('late erlotinib' group). Of the 322 patients randomized to the 'early erlotinib' group, 160 (50%) received second line treatment; of the 321 patients randomized to the 'late erlotinib' group, 250 patients (78%) received second line treatment, until the occurrence of further disease progression death, or unacceptable toxicities.

Recruitment

Patients were recruited at 122 centres in 20 countries globally.

Baseline data

A summary of patient demographics and baseline characteristics are presented in Table 2 and Table 3.

Table 1: Summary of demographic characteristics (ITT population) - Study BO25460 (IUNO)

	Late Erlotinib (N=321)	Early Erlotinib (N=322)
Age (yr)		
n	321	322
Mean (SD)	60.6 (9.1)	60.8 (8.8)
Median	61.0	61.0
Min - Max	30 - 86	26 - 81
Age group (yr)		
n	321	322
< 65	210 (65.4%)	210 (65.2%)
>= 65	111 (34.6%)	112 (34.8%)
Sex		
n	321	322
Male	244 (76.0%)	238 (73.9%)
Female	77 (24.0%)	84 (26.1%)
Race		
n	321	322
Asian	67 (20.9%)	70 (21.7%)
Black or African American	4 (1.2%)	6 (1.9%)
White	249 (77.6%)	244 (75.8%)
Other	1 (0.3%)	2 (0.6%)
Race subcategory		
Asian		
n	67	70
Indian Subcontinent	2 (3.0%)	1 (1.4%)
Other than Indian Subcontinent	65 (97.0%)	69 (98.6%)
Weight (kg) at baseline		
n	321	322
Mean (SD)	71.03 (15.71)	70.14 (14.95)
Median	69.00	68.55
Min - Max	34.1 - 143.0	38.0 - 125.0
Height (cm) at baseline		
n	318	321
Mean (SD)	168.84 (9.35)	168.81 (9.19)
Median	170.00	170.00
Min - Max	140.0 - 190.0	143.0 - 196.0
ECOG PS at baseline		
n	321	322
0	92 (28.7%)	90 (28.0%)
1	229 (71.3%)	232 (72.0%)

Table 2: Summary of NSCLC history (ITT population) - Study BO25460 (IUNO)

	Placebo (N=321)	Erlotinib (N=322)
Cellular classification NSCLC		
n	321	322
Adenocarcinoma	188 (58.6%)	178 (55.3%)
Squamous cell carcinoma	111 (34.6%)	114 (35.4%)
Mixed with predominantly adenocarcinoma component	5 (1.6%)	5 (1.6%)
Mixed with predominantly squamous cell component	5 (1.6%)	1 (0.3%)
Large cell carcinoma	5 (1.6%)	9 (2.8%)
Bronchioalveolar carcinoma	3 (0.9%)	3 (0.9%)
Other	4 (1.2%)	12 (3.7%)
AJCC/ UICC stage		
n	321	322
Stage IIIB	72 (22.4%)	70 (21.7%)
Stage IV	249 (77.6%)	252 (78.3%)
Months Since First Histological Diagnosis of NSCLC to Randomization		
n	321	322
Mean (SD)	5.49 (6.31)	6.48 (11.80)
Median	4.10	3.90
Min - Max	2.8 - 79.0	2.7 - 124.5

AJCC: American Joint Committee on Cancer
UICC: Union for International Cancer Control

Numbers analysed

All 321 patients randomized in the 'late erlotinib' group and all 322 patients randomized in the 'early erlotinib' group were included in the Intent to Treat (ITT) population. Two patients did not receive study treatment post-randomization and were therefore excluded from the safety analysis in the blinded phase.

In total, 71 patients (22%) from the 'late erlotinib' group and 162 patients (50%) from the 'early erlotinib' group were excluded from the safety analysis population in the second-line open-label phase due to not having received at least one dose of open-label phase study treatment.

Outcomes and estimation

Primary endpoint – OS

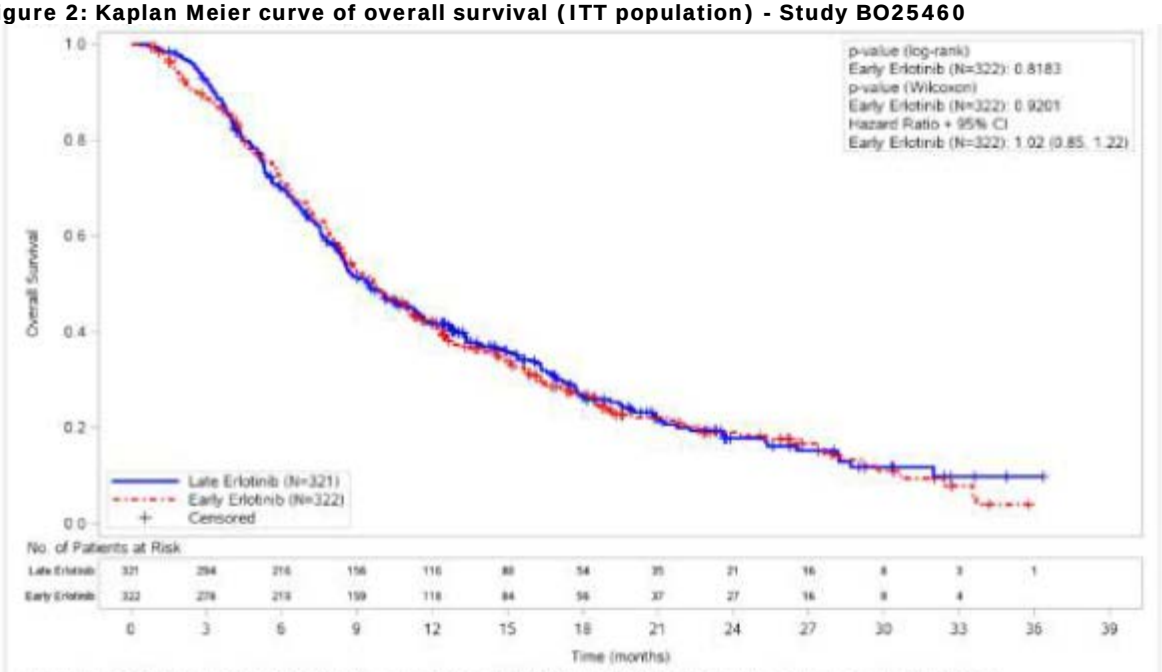
The results of the primary endpoint of this study showed that OS in patients who received 'early erlotinib' in the first-line maintenance setting was not superior to 'late erlotinib' treatment (HR = 1.02; 95% CI: 0.85, 1.22; log rank p-value = 0.8183). Median OS was similar and 1-year event-free rates were the same in both treatment groups.

Table 4: Summary of overall survival (ITT population) - Study BO25460 (IUNO)

	Late Erlotinib (N=321)		Early Erlotinib (N=322)
Patients with event (%)	235 (73.2%)		242 (75.2%)
Patients without event (%)	86 (26.8%)		80 (24.8%)
Time to event (months)			
Median	9.46		9.72
95% CI for Median	(8.38, 11.33)		(8.57, 11.17)
25% and 75%-ile	5.26, 19.45		5.65, 18.53
Range	0.7 to 36.3*		0.4 to 35.8*
Unstratified Analysis			
p-value (log-rank)		0.8183	
Hazard Ratio		1.02	
95% CI		(0.85, 1.22)	
Stratified Analysis			
p-value (log-rank)		0.5256	
Hazard Ratio		1.07	
95% CI		(0.87, 1.32)	
1 year duration			
Patients remaining at risk	116		118
Event Free Rate	41.75		42.15
95% CI for Rate	(36.20, 47.30)		(36.60, 47.70)
Difference in Event Free Rate		-0.40	
95% CI for Difference		(-8.25, 7.45)	
p-value		0.9207	

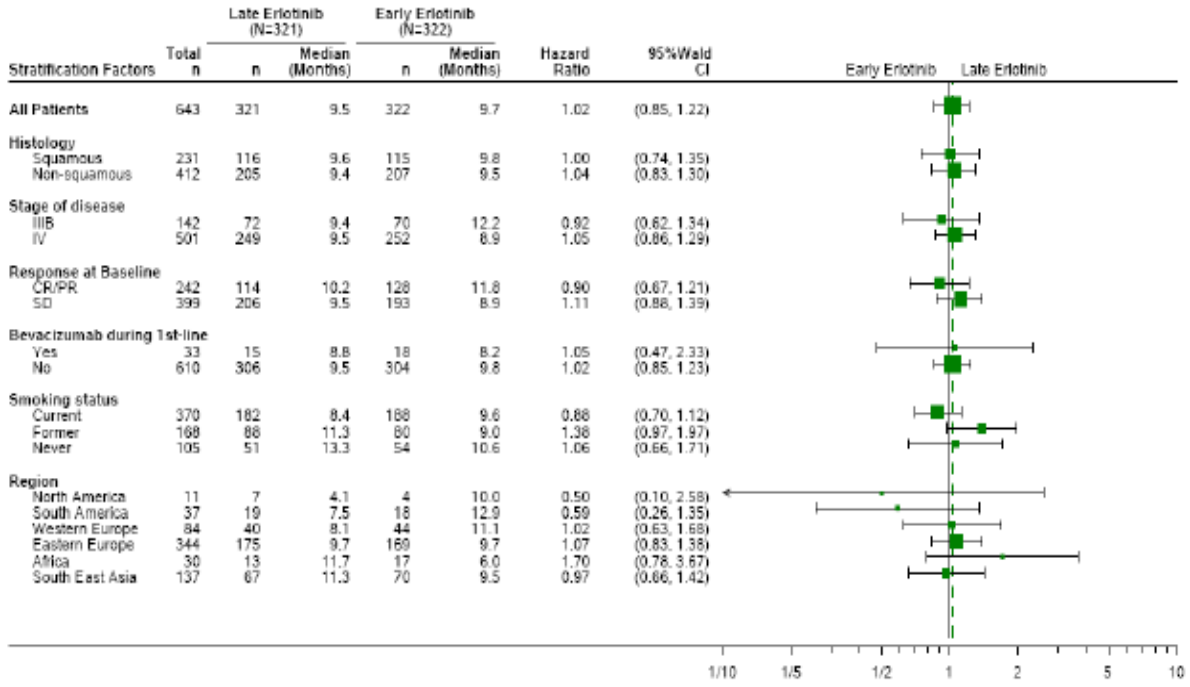
Overall Survival (months) - Censoring: (1=censored, 0=event)
* Censored value
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
For stratified analyses, strata are Histology, Stage, Response, Bevacizumab, Smoking and Region. For unstratified and stratified analyses, Hazard ratios, 95% CIs were estimated by Cox regression without or with the strata.

Figure 2: Kaplan Meier curve of overall survival (ITT population) - Study BO25460



Subgroup analyses

Figure 3: Forest plot of hazard ratios for overall survival by stratification factors (ITT population) - Study BO25460



Median overall survival was estimated from Kaplan-Meier curves.
Hazard ratio relative to Late Erlotinib was estimated by Cox regression. Unstratified hazard ratio is dispayed.

Secondary endpoint - PFS

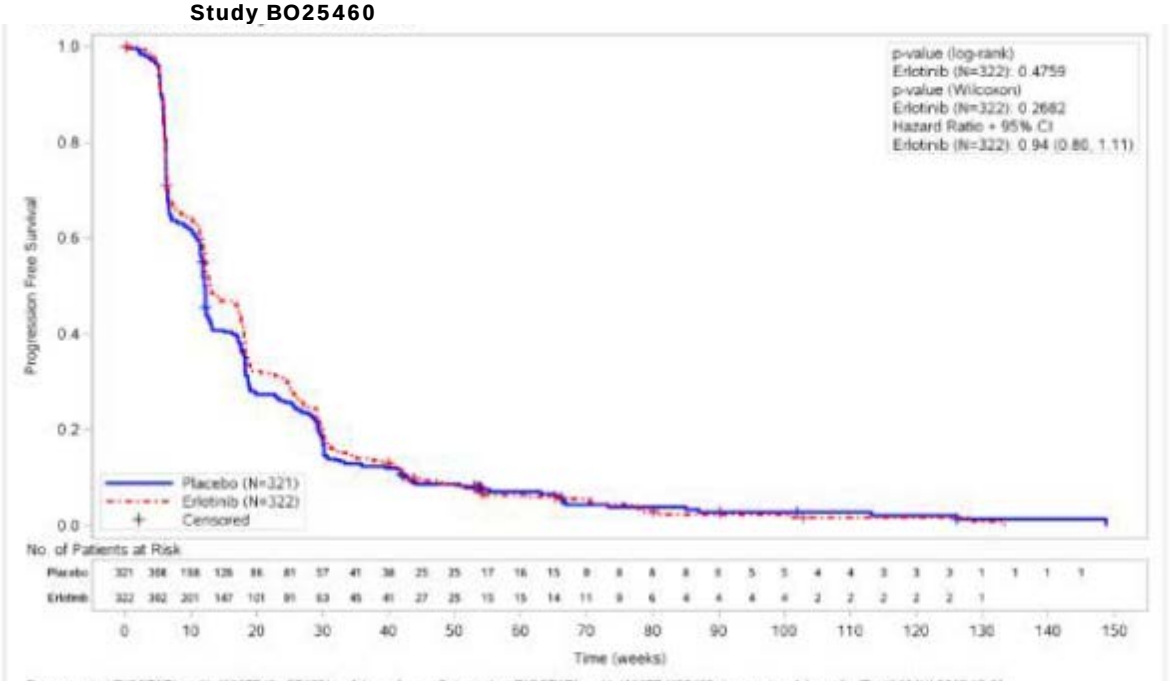
PFS assessed during the blinded phase showed no difference between erlotinib and placebo treatment. At the time of the data cut-off, 305 patients (95.0%) on placebo and 303 patients (94.1%) on erlotinib in the blinded phase, had progressed or died. The majority of these events were progressions (281, placebo and 264, erlotinib). The estimated median PFS was similar for both treatment groups: 12 weeks (95% CI: 11.71, 12.29 weeks [placebo]) versus 13 weeks (95% CI: 12.14, 17.43 weeks [erlotinib]). The HR was 0.94 (95% CI: 0.80, 1.11), showing no clinical meaningful PFS benefit for the erlotinib group (p = 0.48, two-sided unstratified logrank test). The 6-month estimate of PFS rate was 24% (95% CI: 19.50%, 28.94%) in the placebo group compared with 27% (95% CI: 22.19%, 32.02%) in the erlotinib group.

Table 5: Summary of progression-free survival in the blinded phase (ITT population) - Study BO25460

	Placebo (N=321)		Erlotinib (N=322)
Patients with event (%)	305 (95.0%)		303 (94.1%)
Earliest contributing event			
Disease Progression	281		264
Death	24		39
Patients without event (%)	16 (5.0%)		19 (5.9%)
Time to event (weeks)			
Median	12.00		13.00
95% CI for Median	(11.71, 12.29)		(12.14, 17.43)
25% and 75%-ile	6.14, 25.57		6.14, 27.14
Range	0.1* to 148.7		0.1* to 133.3
Unstratified Analysis			
p-value (log-rank)		0.4759	
Hazard Ratio		0.94	
95% CI		(0.80, 1.11)	
Stratified Analysis			
p-value (log-rank)		0.1635	
Hazard Ratio		0.87	
95% CI		(0.72, 1.06)	
6 months duration			
Patients remaining at risk	77		85
Event Free Rate	24.22		27.11
95% CI for Rate	(19.50, 28.94)		(22.19, 32.02)
Difference in Event Free Rate		-2.89	
95% CI for Difference		(-9.70, 3.93)	
p-value		0.4069	

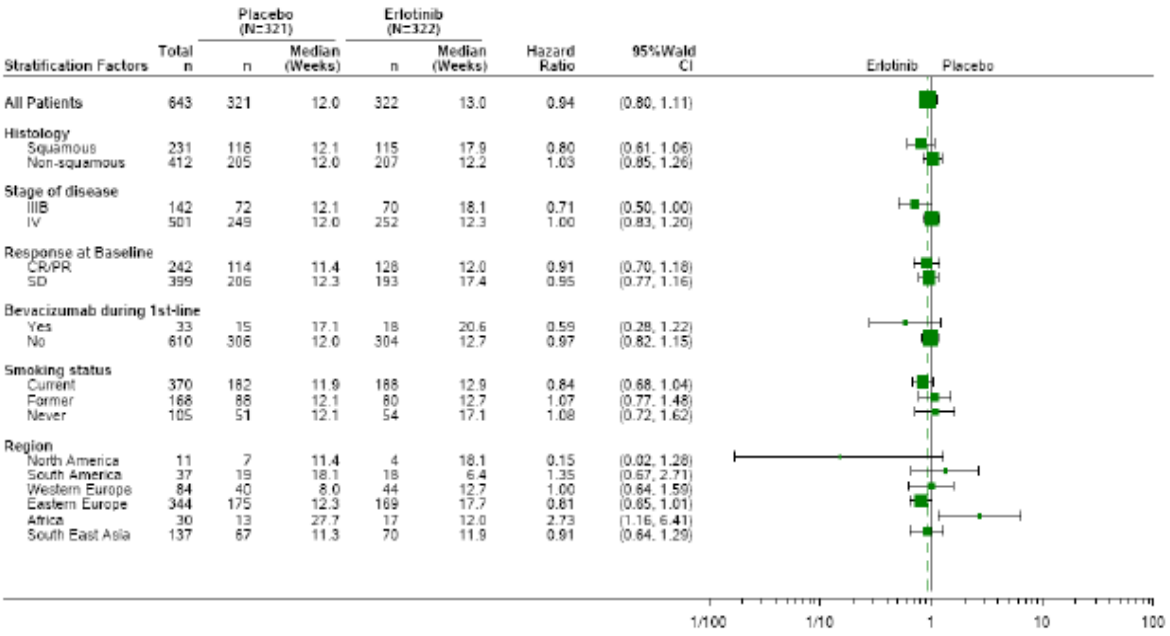
Progression Free Survival (weeks) - Censoring: (1=censored, 0=event)
* Censored value
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
For stratified analyses, strata are Histology, Stage, Response, Bevacizumab, Smoking and Region.
For unstratified and stratified analyses, Hazard ratios, 95% CIs were estimated by Cox regression without or with the strata.

Figure 4: Kaplan-Meier plot for progression-free survival in the blinded phase (ITT population) - Study BO25460



Subgroup analyses

Figure 5: Forest plot of hazard ratios for progression-free survival in the blinded phase by stratification factors (ITT population) - Study BO25460



Median progression-free survival was estimated from Kaplan-Meier curves.
Hazard ratio relative to Placebo was estimated by Cox regression. Unstratified hazard ratio is dispayed.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6: Summary of efficacy for trial IUNO

Title: A multicenter, multinational, randomized, placebo controlled, 2-arm Phase III study designed to evaluate the relative survival benefit and safety of 'early' (first-line maintenance) erlotinib versus 'late' (second-line) erlotinib in patients with advanced (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC whose tumors did not harbor an EGFR-activating mutation and who had not progressed following 4 cycles of platinum-based chemotherapy.			
Study identifier	BO25460		
Design	multicenter, multinational, randomized, placebocontrolled, 2-arm Phase III study		
Hypothesis	Superiority		
Treatments groups	Early erlotinib		150 mg/day erlotinib, n = 322, until PD, death or unacceptable toxicity. If amenable, open-label second-line chemotherapy until PD, death or unacceptable toxicity.
	Late erlotinib		Placebo until PD, death or unacceptable toxicity. If amenable, open-label second-line with 150 mg erlotinib daily p.o until PD, death or unacceptable toxicity
Endpoints and definitions	Primary endpoint	OS	Overall Survival
	Secondary endpoint	PFS	Progression-free survival in the maintenance phase

Database lock	23 March 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Early erlotinib	Late erlotinib
	Number of subject	N=322	N=321
	OS (median in months)	9.72	9.46
	95%CI	8.38, 11.33	8.57, 11.17
	PFS (median in months)	13	12
	95%CI	12.14, 17.43	11.71, 12.29
Effect estimate per comparison	Primary endpoint – OS (stratified analysis)	Comparison groups	Early vs. Late
		Hazard ratio	1.07
		95%CI	0.87, 1.32
		P-value	P = 0.5256
	Secondary endpoint - PFS (stratified analysis)	Comparison groups	Early vs. Late
		Hazard ratio	0.87
		95%CI	0.72, 1.06
		P-value	P = 0.1635

STUDY BO18192 (SATURN): A multi-centre, double-blind randomized, Phase III study to evaluate the efficacy of Tarceva or placebo following 4 cycles of platinum-based chemotherapy in patients with histologically documented, advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) who have not experienced disease progression or unacceptable toxicity during chemotherapy.

Study BO18192 (SATURN) was a randomized, multi-center, Phase III study in patients with histologically documented, locally advanced, or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC before chemotherapy. The results of this study led to the EMA approval (EMEA/H/C/618/II/017; positive opinion received on 18 March 2010) of erlotinib as monotherapy in the maintenance setting in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy.

After eligibility screening, patients with Stage IIIB or IV NSCLC completed four cycles of an acceptable platinum-based chemotherapy combination. Following chemotherapy, patients who met the following criteria were considered eligible for erlotinib treatment: Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1, a life expectancy of at least 12 weeks, adequate hematological, renal, and hepatic function, and absence of unacceptable toxicity and/or disease progression (CR, PR, or SD).

Eligible patients were randomised to receive either erlotinib 150 mg/day or placebo until disease progression, unacceptable toxicity, or death. Randomisation was stratified by EGFR protein expression by IHC, stage of disease at start of chemotherapy, ECOG PS, chemotherapy regimen, smoking status, and region.

The co-primary efficacy endpoints were investigator-assessed PFS according to RECIST in all patients and in the EGFR IHC positive population. An independent combined radiological and clinical assessment was undertaken to provide an independent assessment of response and disease progression. Secondary efficacy endpoints included OS and response rates (ORR and DCR) according to RECIST v1.0.

For the purpose of this Type II variation application, the focus is on the prospectively defined subgroup of patients with EGFR activating mutations (exon 19 deletion or exon 21 L858R mutation). All analyses in this EGFR mutation positive subgroup were prospectively defined, but exploratory in nature. Median survival times and 95% confidence limits for PFS and OS were estimated using Kaplan-Meier methodology, and the corresponding treatment difference tested using a log-rank test. The between-treatment difference in response rates (ORR and DCR) was tested using a $\chi 2$ test.

Progression-Free Survival

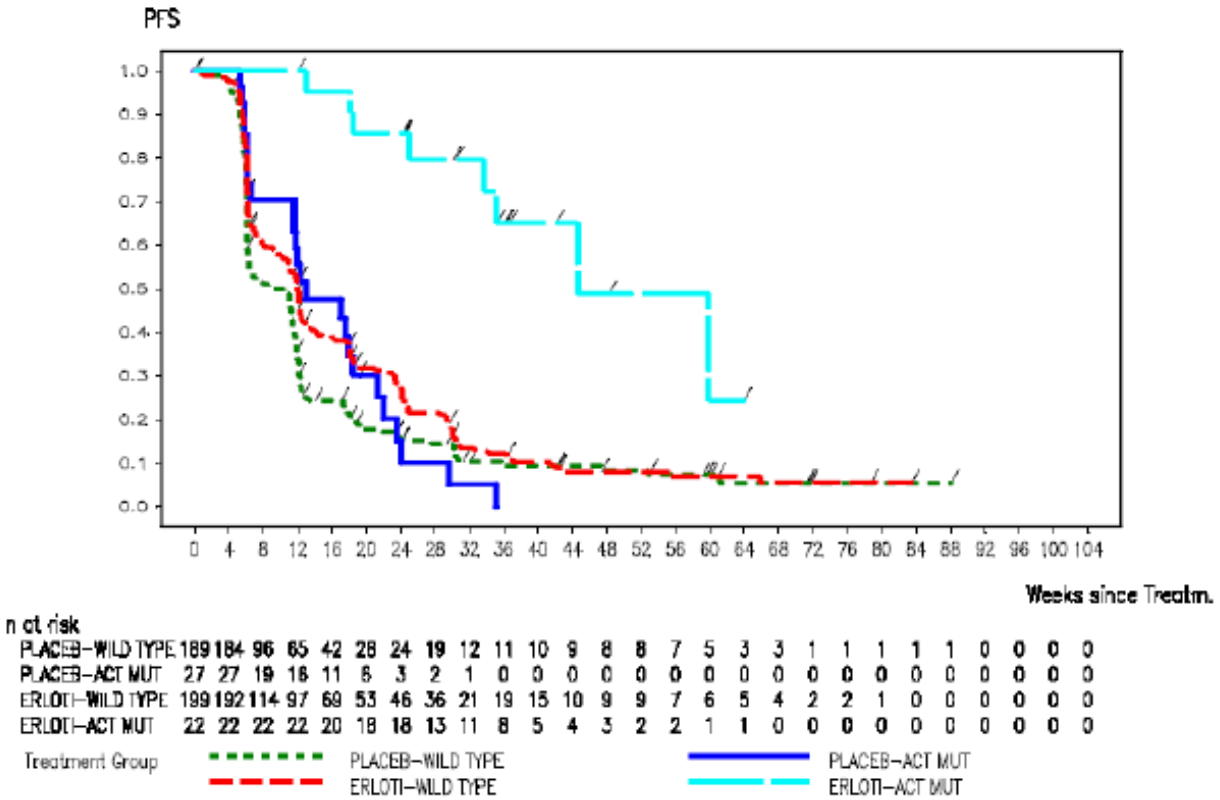
Based on the clinical cut-off for the Clinical Study Report (CSR) (17 May 2008) first-line maintenance erlotinib treatment after 4 cycles of chemotherapy in patients with NSCLC, the overall population showed a benefit for the primary PFS end-point (HR= 0.71 p< 0.0001). However the largest benefit was observed in a predefined exploratory analysis in patients with EGFR activating mutations (n= 49) demonstrating a substantial PFS benefit (HR=0.10, 95% CI, 0.04 to 0.25; p<0.0001). Median PFS was 44.6 weeks (95% CI: 35.1 weeks, not reached) in the erlotinib group compared with 13.0 weeks (95% CI: 11.6, 18.4 weeks) in the placebo group. A Kaplan-Meier curve of the PFS results for patients with both EGFR mutated and wild-type tumours is shown in the below figure. The Kaplan-Meier curves for PFS for the subpopulation of patients with EGFR mutations were separated between the erlotinib and placebo groups over the course of the observation period.

Table 7: Summary of PFS in the EGFR mutation positive subgroup (cut-off 17 May 2008) - Study BO18192

	PLACEBO (N=27)		ERLOTINIB (N=22)
Patients with event	24 (88.9 %)		8 (36.4 %)
Patients without event*	3 (11.1 %)		14 (63.6 %)
Time to event (weeks)			
Median#	13.0		44.6
95% CI for Median#	[11.6;18.4]		[35.1;.]
25% and 75%-ile	6.1;22.0		33.7;59.9
Range##	5.3 to 35.1		12.1 to 64.0
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.10	
95% CI		[0.04;0.25]	
6 months estimate			
Patients remaining at risk	2		13
Event Free Rate#	0.10		0.80
95% CI for Rate#	[0.00;0.23]		[0.62;0.98]

PFS [weeks] (TTPFS_W) - Censoring: PFS Censoring (prim. ana.,1=PD/death) (CSPFS)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 17MAY2008

Figure 6: Kaplan-Meier curves of PFS by trial treatment and EGFR mutation status (cut-off 17 May 2008) - Study BO18192



Overall Survival

At the time of data cut-off (17 May 2009), there was a benefit in OS (HR= 0.81 p=0.0088) in the overall population. 8 of 22 patients (36.4%) with tumors harboring EGFR-activating mutations in the erlotinib group had died, therefore the OS data reported at this time were immature. In addition, 67% of placebo patients

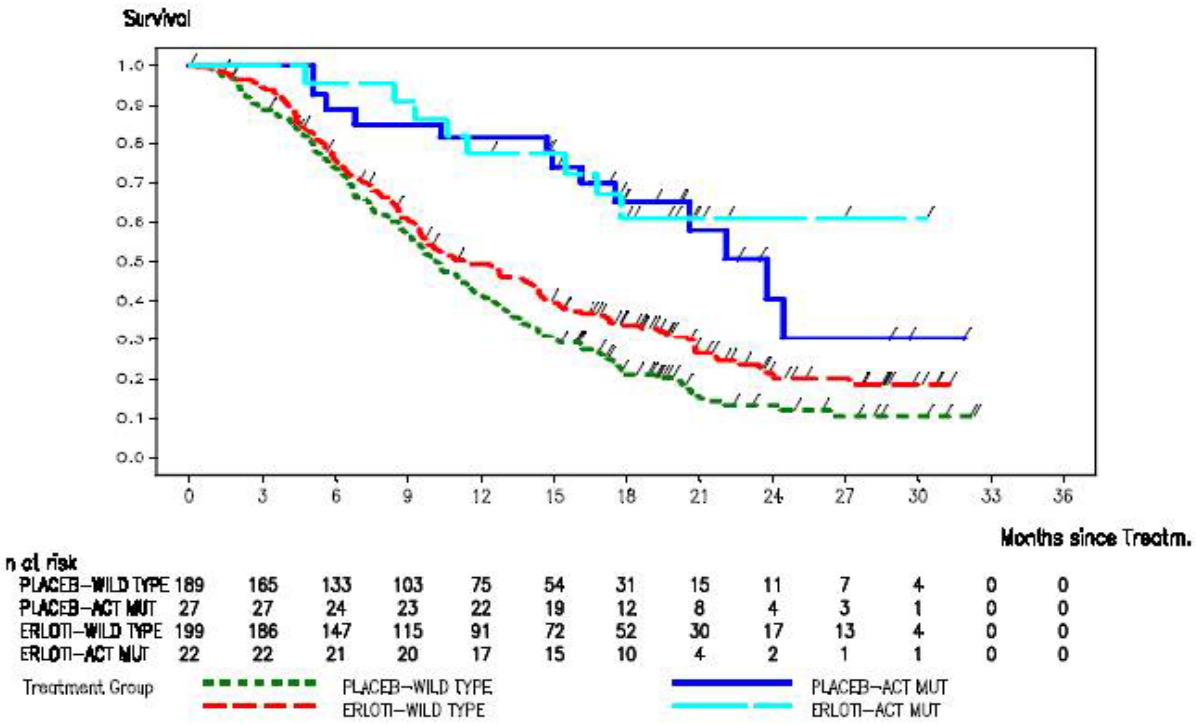
in the EGFR mutation positive subgroup received second or further line treatment with EGFR-tyrosine kinase inhibitors (TKIs), which may have affected the observed hazard ratio for OS. Nonetheless, the HR for OS in patients with activating EGFR mutations was below 1.00 (HR = 0.83; 95% CI: 0.34, 2.02).

Table 8: Summary of OS in the EGFR mutation positive subgroup (cut-off 17 May 2009) - Study BO18192

	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

Figure 7: Kaplan-Meier curves of OS by trial treatment and EGFR mutation status (cut-off 17 May 2009) - Study BO18192



In an updated analysis of OS (data cut-off 12 Jan 2012), no difference was observed in the risk of death between the two treatment groups in the subgroup of patients with tumours harboring an EGFR-activating mutation. The HR for OS was 1.01 (95% CI: 0.52; 1.97), the p-value (log-rank test) was 0.9739 and the median OS was 23.8 and 23.6 months in the placebo and erlotinib groups, respectively.

Analysis performed across trials (pooled analyses and meta-analysis)

In the Liu et al. 2015 meta-analysis of more than 1592 patients with advanced NSCLC and EGFR activating mutations from 27 randomized controlled studies with first generation EGFR-TKIs (erlotinib or gefitinib), pooled estimates of treatment efficacy were calculated based on published HRs or estimated from other survival data.

The analysis of PFS in patients receiving EGFR-TKIs or placebo as maintenance therapy included data from three clinical studies (including the BO18192 [SATURN] subgroup). Results in patients with EGFR activating mutations were consistent with the findings from SATURN, revealing a significant PFS benefit for first-line maintenance treatment with erlotinib versus placebo (HR [95% CI]: 0.14 [0.08, 0.26], p= 0.00001). Patients without an EGFR activating mutation had an HR (95% CI) of 0.81 (0.68, 0.97), p= 0.02. Other findings of this meta-analysis included the following:

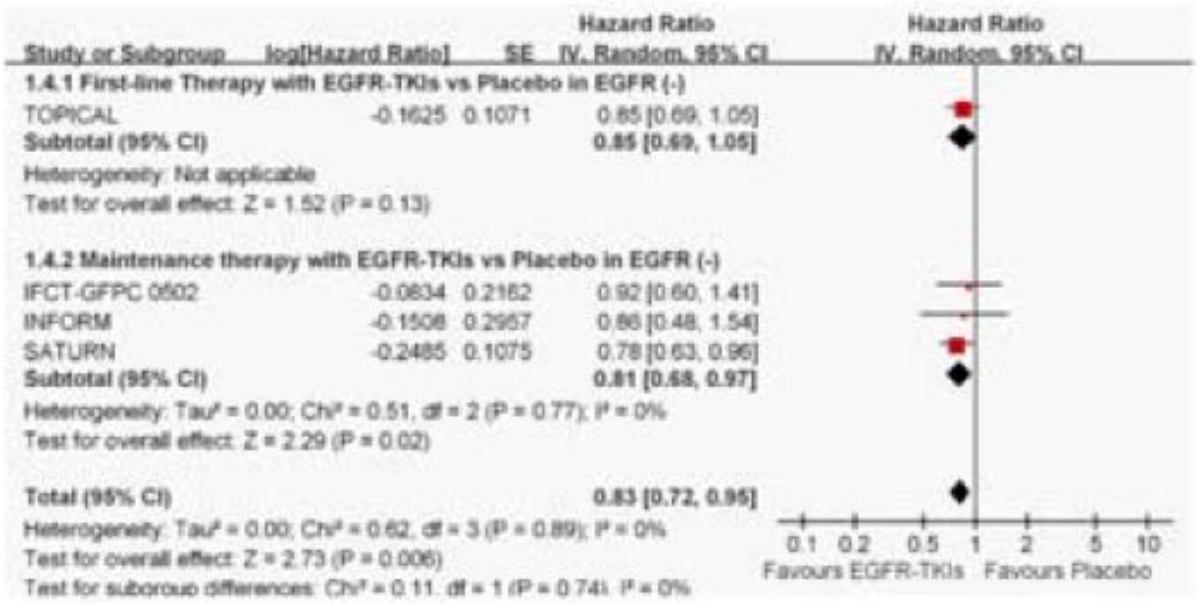
- In patients with EGFR activating mutations, treatment with an EGFR-TKI showed a PFS benefit over treatment with chemotherapy in the first-line setting (HR [95% CI]: 0.41 [0.31, 0.55], p=0.00001) and in the second/third-line setting (HR [95% CI]: 0.46 [0.24, 0.89], p=0.02). For patients without a mutation, PFS was reduced with an EGFR-TKI compared with chemotherapy in the first-line (HR [95% CI]: 1.65 [1.06, 2.58], p=0.03) and second/third-line setting (HR [95% CI]: 1.27 [1.08, 1.51], p=0.005).
- A significant difference (p=0.04) in PFS improvement between patients with and without a mutation could also be seen for treatment with an EGFR-TKI versus placebo (four clinical studies) (HR [95% CI]: 0.26 [0.09, 0.79], p=0.02 for patients with a mutation and 0.83 [0.72, 0.95], p=0.006 for patients without a mutation), suggesting a greater PFS benefit of EGFR-TKIs as first-line and second/third-line treatment in patients with EGFR activating mutations compared with patients without a mutation.
- Patients treated with EGFR-TKIs plus chemotherapy (five clinical studies) had a more pronounced PFS benefit compared with chemotherapy alone (HR [95% CI]: 0.49 [0.32, 0.77], p=0.002 for patients with a mutation and 0.83 [0.71, 0.96], p=0.01 for patients without a mutation). The heterogeneity between the two subpopulations was significant (p =0.03).

Overall, the authors suggest that a treatment benefit with EGFR-TKIs could be shown for patients with EGFR activating mutations irrespective of the treatment setting.

The meta-analysis by *Liu et al.* included, amongst others, three studies in the maintenance setting, where an EGFR-TKI is compared with placebo:

1) IFCT-GFPC with 8 patients with EGFR activating mutation (Erlotinib vs. Placebo)
2) INFORM with 30 patients with EGFR activating mutation (Gefitinib vs. placebo)
3) SATURN with 49 patients with EGFR activating mutation

Figure 8: Summary of the meta-analysis of first-line therapy and maintenance therapy with EGFR-TKIs



The authors pooled the three above studies and could show a statistically significant HR, but the results seem to be mainly driven by the SATURN study. Nonetheless, altogether data from the three studies provide evidence for the effect of EGFR-TKI's in the maintenance setting.

Pooled Analysis of Published Clinical Study Data[4]

The Paz-Ares et al. 2014 pooled analysis of prospective or retrospective studies evaluated treatment with single agent EGFR-TKIs (erlotinib or gefitinib) or chemotherapy in patients with NSCLC with EGFR activating mutations. The pooled median PFS was evaluated in 26 studies (731 patients) with erlotinib, 54 studies (1802 patients) with gefitinib, and 20 studies (984 patients) with chemotherapy. The results of the analysis indicated that the PFS (bootstrap estimated 95% confidence limit) was longer in patients when treated with erlotinib (12.4 months [10.9, 13.4 months]), or gefitinib (9.4 months [8.7, 10.2 months]) compared with conventional chemotherapy (5.6 months [5.1, 6.2 months]). Permutation testing with 20,000 random permutations indicated that the increase in PFS was statistically significant for erlotinib or gefitinib compared with chemotherapy in the first-line, in lines other than first-line (p=0.0022 and p=0.0039, respectively), and in all lines of therapy. Pooled median PFS values for erlotinib were not statistically different between lines of therapy (12.0 vs. 12.9 months for first-line vs. other lines, p=0.678). Overall, the Applicant claim that a clear PFS benefit was reported with an EGFR-TKI compared with chemotherapy for NSCLC patients with EGFR activating mutations in all lines of treatment.

Supportive study

The Atlas study: randomized, Double-blind, Placebo-controlled Phase IIIB Study

The ATLAS study[1] explored the potential benefit of adding maintenance erlotinib to bevacizumab after a first-line chemotherapy regimen with bevacizumab in 743 patients with advanced NSCLC, including 52 patients with EGFR activating mutations (27 with bevacizumab/erlotinib and 25 with bevacizumab/placebo). Patients were eligible if they showed stable disease or no significant toxicity after four lines of chemotherapy.

In the mutation-positive population, biomarker analyses showed a greater improvement in PFS with bevacizumab/erlotinib versus bevacizumab/placebo (HR [95% CI] 0.44 [0.22, 0.86]) compared with patients without an EGFR activating mutation (n=295; 150 bevacizumab/erlotinib and 145 bevacizumab/placebo) (HR [95% CI]: 0.85 [0.64, 1.13]).

More than 50% of patients in each group had subsequent second-line therapy. Despite this, OS results showed a similar difference in outcome between the combination with erlotinib and with placebo by EGFR mutation status: HR (95% CI): 0.46 (0.21, 1.02) for patients with EGFR activating mutations and 0.86 (0.65, 1.15) for patients without an EGFR activating mutation.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The IUNO study was designed at the request of regulatory authorities to investigate "early erlotinib" vs. "late erlotinib". Patients without PD after 4 cycles of platinum-based chemotherapy were randomised to erlotinib 150mg/day or placebo until PD, death or unacceptable toxicity. The aim of this study was to investigate the efficacy of erlotinib in maintenance therapy in patients with NSCLC and no known EGFR activating mutation. 321 patients were randomised to receive placebo and 322 were randomised to receive erlotinib. The primary endpoint was OS and secondary endpoints were PFS, ORR, DCR (disease control rate), and safety. The IUNO study had a blinded phase, which was the time from randomisation to PD. After PD the study was un-blinded. Patients in the placebo arm would then switch to erlotinib and patients in the erlotinib arm would switch to second-line chemotherapy or BSC. The primary endpoint was assessed using a 2-sided stratified log-rank test at 5% significance level.

The baseline characteristics are well-balanced between the two groups. The majority of the patients were male, white, ECOG PS 1, had adenocarcinoma or squamous cell carcinoma and stage IV disease.

The SATURN study had been previously assessed by the CHMP (Doc. Ref No. EMA/CHMP/298837/2010) and was the basis for the maintenance indication. Therefore, a re-assessment of this study was not performed in this variation. However, a discussion of the updated data from the subgroup of patients with EGFR activating mutation was assessed.

Efficacy data and additional analyses

The primary endpoint in the IUNO study shows no difference between the two groups (HR = 1.02; 95% CI: 0.85, 1.22; p-value = 0.8183). Thus, there seems to be no benefit of early erlotinib treatment in patients with NSCLC with no known EGFR activating mutation. The subgroup analysis shows the HR in the different subgroups is not different from the overall estimate. Some subgroups (North America and Eastern Europe) have HR that are very different from the overall estimate, however, the 95%CIs are very wide reflecting the small number of patients in these subgroups. The results of the PFS analysis are consistent with the OS data.

Thus, the indication of "maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy." is no longer justified.

However, following the SAG recommendations in 2010 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. An updated analysis of PFS in this subgroup confirms the previous findings. The use of erlotinib as maintenance after first line treatment shows no detrimental effect on OS in the subgroup of patients with EGFR activating mutations. The KM curves are overlapping. This is somewhat expected, since any effect of erlotinib on OS is bound to be diluted by cross-over and later lines of therapy.

To further support the use of erlotinib in the maintenance setting in patients with EGFR activating mutations, the Applicant has provided analyses of three published studies. The ATLAS study investigated the efficacy of bevacizumab+erlotinib vs. bevacizumab+placebo in the maintenance setting in patients with stable disease after first line treatment. Known EGFR mutation status was not required for inclusion and was not a stratification factor. In total 373 patients were randomised to bevacizumab +placebo and 370 patients were randomized to bevacizumab +erl. A biomarker analysis identified 52 patients in total (27 patients in the bevacizumab +erl and 25 patiens in the bevacizumab +placebo) with EGFR activating mutations. The PFS

was statistically significant in favour of patients with EGFR activating mutation being treated with bevacizumab +erl compared to those with EGFR activating mutation being treated with bevacizumab+placebo (HR = 0.44). This is reassuring and provides further supportive evidence for the findings in the SATURN study in this subpopulation. The results showed no detrimental effect on OS.

The meta-analysis by Lui et al. included, amongst others, three studies in the maintenance setting, where EGFR-TKIs were compared with placebo. The authors pooled the three studies and could show a statistically significant HR, but the results seem to be mainly driven by the SATURN study. Nonetheless, the data from the three studies provide further evidence for the effect of EGFR-TKI's in the switch maintenance setting for patients with EGFR-activating mutations.

The last supportive study, the Paz-Ares study, analysed both prospective and retrospective studies. The study provided evidence for the efficacy of EGFR-TKI's in first-line and other lines of therapy, however, did not provide any direct evidence for the use of erlotinib in maintenance setting.

In light of the results from the IUNO study and other available information on erlotinib, the MAH is recommended to discuss the use of erlotinib for the treatment of patients without EGFR activating mutation status with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

2.4.3. Conclusions on the clinical efficacy

The efficacy of erlotinib in patients with advanced NSCLC with EGFR activating mutation has previously been demonstrated in clinical trials (e.g. EURTAC, EMA/657134/2011). However, the indication of "switch maintenance use of erlotinib in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum based first line chemotherapy" is no longer justified based on the findings in the IUNO study. The study failed to meet its primary endpoint, OS. However, the efficacy of erlotinib in the maintenance setting in the subgroup of patients with EGFR activating mutation has previously been shown in exploratory analysis in the SATURN study. Updated analysis of the SATURN trial support these previous findings. Recent scientific publications provide further evidence on the efficacy of erlotinib in the maintenance setting in patients with EGFR activating mutation. In line with the findings in the SATURN study, large improvements in PFS in the maintenance setting in patients with EGFR activating mutation were observed in the ATLAS study. Based on the SATURN study, switch maintenance treatment was considered justified in patients with stable disease after first-line treatment.

Overall, taking the totality of data and the biological rationale for the use of erlotinib in EGFR mutated patients into consideration, the use of erlotinib in the switch maintenance setting in patients with NSCLC with EGFR activating mutation with stable disease after first-line chemotherapy treatment is considered justified.

2.5. Clinical safety

Introduction

The SATURN study has previously been evaluated by the CHMP. However, the safety in the subgroup of patients with EGFR activating mutation will be subject to an assessment.

The safety data from the IUNO study will also be described in this section.

Adverse events

STUDY BO18192 (SATURN) Overall, the safety profile of erlotinib in patients with NSCLC whose tumors harbored EGFR-activating mutations was consistent with previously observed data. An overview of key safety data reported in the EGFR mutant subpopulation of the BO18192 (SATURN) study based on the Clinical Study Report cut-off date is presented in the below table, and detailed results are described in the following sections.

Table 9: Summary of safety in the EGFR mutation positive subgroup - Study BO18192

	PLACEBO N = 26 No. (%)	ERLOTINIB N = 22 No. (%)
Total Pts with at Least one AE	12 (46.2)	20 (90.9)
Total Number of AEs	43	141
Deaths #	1 (3.8)	1 (4.5)
Study withdrawals due to an AE #	0 (0.0)	0 (0.0)
Patients with at least one		
AE leading to Death	0 (0.0)	0 (0.0)
Serious AE	0 (0.0)	1 (4.5)
Related serious AE	0 (0.0)	0 (0.0)
AE leading to withdrawal from treatment	0 (0.0)	0 (0.0)
AE leading to dose modification/interruption	1 (3.8)	4 (18.2)
Related AE	5 (19.2)	19 (86.4)
Related AE leading to withdrawal from treatment	0 (0.0)	0 (0.0)
Severe AE	1 (3.8)	6 (27.3)

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

Common AEs

Table 10: Summary of common adverse events occurring in ≥10% of patients in the EGFR mutation positive subgroup - Study BO18192

Body System/ Adverse Event	PLACEBO N = 26 No. (%)	ERLOTINIB N = 22 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	12 (46.2)	20 (90.9)
Total Number of AEs	43	141
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	4 (15.4)	18 (81.8)
RASH	1 (3.8)	10 (45.5)
PRURITUS	2 (7.7)	3 (13.6)
ACNE	-	3 (13.6)
DERMATITIS ACNEIFORM	-	3 (13.6)
DRY SKIN	-	3 (13.6)
SKIN FISSURES	-	3 (13.6)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	7 (26.9)	12 (54.5)
DIARRHOEA	3 (11.5)	8 (36.4)
NAUSEA	3 (11.5)	4 (18.2)
VOMITING	2 (7.7)	3 (13.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	4 (15.4)	9 (40.9)
COUGH	1 (3.8)	5 (22.7)
DYSPNOEA	1 (3.8)	4 (18.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	6 (23.1)	5 (22.7)
FATIGUE	2 (7.7)	3 (13.6)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	1 (3.8)	9 (40.9)
PARONYCHIA	-	3 (13.6)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	3 (11.5)	5 (22.7)
HEADACHE	1 (3.8)	4 (18.2)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	1 (3.8)	4 (18.2)
ANOREXIA	-	3 (13.6)
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	-	4 (18.2)
INSOMNIA	-	3 (13.6)

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

Serious AEs and deaths

Table 11: Summary of serious adverse events in the EGFR mutation positive subgroup - Study BO18192

Body System/ Adverse Event	PLACEBO N = 26 No. (%)	ERLOTINIB N = 22 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	-	1 (4.5)
Total Number of AEs	-	1
CARDIAC DISORDERS		
Total Pts With at Least one AE	-	1 (4.5)
LEFT VENTRICULAR DYSFUNCTION	-	1 (4.5)
Total Number of AEs	-	1

Investigator text for Adverse Events encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 17MAY2008
AE11 27JUL2009:12:58:12 (1 of 1)

At the time of the clinical cut-off for the updated overall survival (OS) analysis, 8 patients in the erlotinib treatment group and 12 patients in the placebo group in the subpopulation of patients with EGFR activating mutations had died during the treatment period. All 21 patients had died due to disease progression (data available on request).

STUDY BO25460 (IUNO)

Table 12: Summery of adverse events with an incidence of at least 3% during the blinded phase - Study BO25460

Cut-off for statistical analysis: 23MAR2015

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=319)	Erlotinib (N=322)
RASH	32 (10.0%)	127 (39.4%)
DRY SKIN	7 (2.2%)	13 (4.0%)
PRURITUS	3 (0.9%)	17 (5.3%)
RASH MACULO-PAPULAR	3 (0.9%)	17 (5.3%)
ACNE	1 (0.3%)	10 (3.1%)
DIARRHOEA	14 (4.4%)	78 (24.2%)
NAUSEA	14 (4.4%)	17 (5.3%)
VOMITING	8 (2.5%)	11 (3.4%)
COUGH	37 (11.6%)	31 (9.6%)
DYSPNOEA	23 (7.2%)	27 (8.4%)
HAEMOPTYSIS	7 (2.2%)	13 (4.0%)
FATIGUE	21 (6.6%)	21 (6.5%)
CHEST PAIN	11 (3.4%)	17 (5.3%)
ASTHENIA	11 (3.4%)	16 (5.0%)
PYREXIA	5 (1.6%)	10 (3.1%)
DECREASED APPETITE	11 (3.4%)	21 (6.5%)
HEADACHE	14 (4.4%)	8 (2.5%)
WEIGHT DECREASED	7 (2.2%)	12 (3.7%)
ANAEMIA	8 (2.5%)	10 (3.1%)
ARTHRALGIA	11 (3.4%)	2 (0.6%)

Investigator text for AEs encoded using MedDRA version 18.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

Serious adverse event / deaths / other significant events

Table 3: Summary of serious adverse events in the blinded phase - BO25460

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=319)	Erlotinib (N=322)
Total number of patients with at least one adverse event	27 (8.5%)	36 (11.2%)
Overall total number of events	34	47
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	5 (1.6%)	9 (2.8%)
Total number of events	5	10
PULMONARY EMBOLISM	0	4 (1.2%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	3 (0.9%)	0
HAEMOPTYSIS	0	2 (0.6%)
INTERSTITIAL LUNG DISEASE	0	2 (0.6%)
PLEURAL EFFUSION	0	1 (0.3%)
PLEURITIC PAIN	1 (0.3%)	0
PNEUMONIA ASPIRATION	0	1 (0.3%)
RESPIRATORY FAILURE	1 (0.3%)	0
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	6 (1.9%)	7 (2.2%)
Total number of events	7	9
PNEUMONIA	3 (0.9%)	4 (1.2%)
ABSCESS ORAL	1 (0.3%)	0
LOBAR PNEUMONIA	1 (0.3%)	0
PERITONITIS	0	1 (0.3%)
PHARYNGITIS	0	1 (0.3%)
RESPIRATORY TRACT INFECTION	0	1 (0.3%)
SEPTIC SHOCK	1 (0.3%)	0
URINARY TRACT INFECTION	1 (0.3%)	0
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	3 (0.9%)	5 (1.6%)
Total number of events	3	5
CEREBROVASCULAR ACCIDENT	0	2 (0.6%)
CEREBRAL ISCHAEMIA	1 (0.3%)	0
DIZZINESS	0	1 (0.3%)
HYDROCEPHALUS	1 (0.3%)	0
HYPOGLYCAEMIC COMA	0	1 (0.3%)
PARAPARESIS	1 (0.3%)	0
SYNCOPE	0	1 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total number of patients with at least one adverse event	4 (1.3%)	3 (0.9%)
Total number of events	5	4
FEMUR FRACTURE	1 (0.3%)	0
FRACTURE	0	1 (0.3%)
HIP FRACTURE	1 (0.3%)	0
ILIUM FRACTURE	1 (0.3%)	0
LIMB INJURY	0	1 (0.3%)
SPINAL COMPRESSION FRACTURE	1 (0.3%)	0
SUBDURAL HAEMATOMA	0	1 (0.3%)
TRACHEAL OBSTRUCTION	1 (0.3%)	0
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	1 (0.3%)	4 (1.2%)
Total number of events	1	4
CARDIO-RESPIRATORY ARREST	0	1 (0.3%)
CARDIOPULMONARY FAILURE	0	1 (0.3%)
MYOCARDIAL INFARCTION	0	1 (0.3%)
PERICARDIAL EFFUSION	1 (0.3%)	0
VENTRICULAR EXTRASYSTOLES	0	1 (0.3%)

GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	1 (0.3%)	4 (1.2%)
Total number of events	1	6
DIARRHOEA	0	2 (0.6%)
GASTRITIS EROSIVE	0	1 (0.3%)
HAEMORRHOIDS THROMBOSED	1 (0.3%)	0
NAUSEA	0	1 (0.3%)
VOMITING	0	1 (0.3%)
VASCULAR DISORDERS		
Total number of patients with at least one adverse event	4 (1.3%)	0
Total number of events	4	0
DEEP VEIN THROMBOSIS	1 (0.3%)	0
HYPOTENSION	1 (0.3%)	0
SUPERIOR VENA CAVA SYNDROME	1 (0.3%)	0
THROMBOSIS	1 (0.3%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	1 (0.3%)	2 (0.6%)
Total number of events	1	2
ANAEMIA	1 (0.3%)	2 (0.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	3 (0.9%)	0
Total number of events	3	0
FATIGUE	2 (0.6%)	0
ASTHENIA	1 (0.3%)	0
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	2 (0.6%)	1 (0.3%)
Total number of events	2	1
DEHYDRATION	1 (0.3%)	0
DIABETES MELLITUS	1 (0.3%)	0
METABOLIC ACIDOSIS	0	1 (0.3%)
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.6%)
Total number of events	0	3
CONFUSIONAL STATE	0	2 (0.6%)
DEPRESSION	0	1 (0.3%)
RENAL AND URINARY DISORDERS		
Total number of patients with at least one adverse event	2 (0.6%)	0
Total number of events	2	0
ACUTE KIDNEY INJURY	1 (0.3%)	0
URINARY RETENTION	1 (0.3%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
OSTEONECROSIS OF JAW	0	1 (0.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
SKIN MASS	0	1 (0.3%)
SURGICAL AND MEDICAL PROCEDURES		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
FINGER AMPUTATION	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 18.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Deaths

For the IUNO study, there were 36 deaths during the blinded phase, 25 in the erlotinib group and 11 in the placebo group; in total 22 deaths were due to progressive disease (PD) and 14 deaths were due to adverse events. More patients on erlotinib died due to PD in the blinded phase compared to on placebo (14/322 [4.3%] vs. 8/319 [2.5%]) and the majority of these deaths on erlotinib occurred within 12 weeks from randomization (2.5% [8/14] vs. 0.9% [3/8] on placebo), although one of the protocol inclusion criteria mandated that the patient's life expectancy should have been at least 12 weeks from randomization to be included in the study. A similar proportion of patients died due to PD in the remainder of the blinded phase (1.9% [6/322] of patients on erlotinib vs. 1.6% [5/319] of patients on placebo).

Table 4: Overview of deaths in the blinded phase - BO25460

Cause of Death	Placebo (N=319)	Erlotinib (N=322)
Total No. of Deaths	11	25
Progression of Disease	8 (72.7%)	14 (56.0%)
Adverse Events	3 (27.3%)	11 (44.0%)

Including patients with death due to blinded phase adverse event and patients with death reported in blinded phase completion/early discontinuation form if the death is due to reason other than adverse event.

There were more deaths due to AEs (defined as events that may not be attributed exclusively due to the progression of underlying malignancy) in the erlotinib group (11 patients [3.4%]) compared with the placebo group (3 patients [0.9%). The majority of these deaths were similarly within the first 12 weeks postrandomisation (6/11 on erlotinib vs. 2/3 on placebo). None of the fatal events were considered causally related to blinded phase study drug by the investigators; rather, the majority was considered related to NSCLC and/or concurrent disease/concomitant medications (3 events) and 'other' undefined causes (4 events).

Table 5: Listing of deaths due to adverse events in the blinded phase – BO25460

Patient	Age	Sex	Race	Day of Death	AE Leading to Death	Related (yes/no)
Placebo						
		M	Asian	250	lobar pneumonia	no
		M	White	21	hydrocephalus	no
		M	Asian	63	respiratory failure	no
Erlotinib						
		M	White	72	pulmonary embolism	no
		M	White	99	pulmonary embolism	no
		M	White	52	pulmonary embolism	no
		F	White	60	pneumonia	no
		F	White	132	pneumonia	no
		M	Asian	176	pneumonia aspiration	no
		M	White	30	cardiorespiratory arrest	no
		M	White	195	cardiopulmonary failure	no
		F	Asian	51	cerebrovascular accident	no
		M	Asian	52	metabolic acidosis	no
		M	White	176	hemoptysis	no

Laboratory findings

Hematology laboratory parameters were only assessed as clinically needed during the BO25460 (IUNO) study. Mean and median hematology and chemistry parameters were within the normal range and generally comparable among patients in both treatment groups.

Discontinuation due to adverse events

Table 6: Summery of adverse events leading to study drug withdrawal during the blinded phase - Study BO25460

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=319)	Erlotinib (N=322)
Total number of patients with at least one adverse event	3 (0.9%)	10 (3.1%)
Overall total number of events	3	17
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	0	5 (1.6%)
Total number of events	0	5
DYSPNOEA	0	2 (0.6%)
INTERSTITIAL LUNG DISEASE	0	2 (0.6%)
HAEMOPTYSIS	0	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	1 (0.3%)	3 (0.9%)
Total number of events	1	3
FATIGUE	0	3 (0.9%)
ASTHENIA	1 (0.3%)	0
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	0	3 (0.9%)
Total number of events	0	3
ABDOMINAL PAIN	0	2 (0.6%)
DYSPHAGIA	0	1 (0.3%)
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	0	2 (0.6%)
Total number of events	0	2
ACTINOMYCOSIS	0	1 (0.3%)
PERITONITIS	0	1 (0.3%)
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.6%)
Total number of events	0	2
DECREASED APPETITE	0	2 (0.6%)
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
MYOCARDIAL INFARCTION	0	1 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
SPINAL PAIN	0	1 (0.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total number of patients with at least one adverse event	1 (0.3%)	0
Total number of events	1	0
NON-HODGKIN'S LYMPHOMA	1 (0.3%)	0
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	1 (0.3%)	0
Total number of events	1	0
CEREBRAL ISCHAEMIA	1 (0.3%)	0

Investigator text for AEs encoded using MedDRA version 18.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

2.5.1. Discussion on clinical safety

The safety profile of patients with EGFR activating mutation is consistent with the findings for the entire population in the SATURN study. Although the number of patients is low, no concerns have been raised. The most common AEs are skin disorders (rash) and diarrhoea. These are well-known AEs related to the use of erlotinib and are clinically manageable. There are no major differences with regard to the number of deaths. Only one SAE (left ventricular dysfunction) occurred in the erlotinib arm and none in the placebo arm. The event resolved with following treatment.

With regard to the IUNO, key safety data from the blinded phase of the study have been assessed. The most common AEs in the erlotinib arm are rash, diarrhoea, dyspnea and cough. The above pattern in AEs is in line with the known safety profile of erlotinib in patients with NSCLC. The number of deaths during the firsts 12 weeks was higher in the erlotinib arm due to an imbalance with regard to patients with a short life expectancy. In the remainder of the blinded phase, the number of deaths was comparable. During the blinded phase more deaths due to AEs are observed in the erlotinib arm. Six out of 11 deaths in the erlotinib

arm occurred during the first 12 weeks and may thus have been related to the imbalance in patients with a short life expectancy. Most of the AEs seem to be related to the underlying disease. However, severe infections, such as pneumonia with or without neutropenia, has been observed in other clinical trials. Furthermore, cases of interstitial lung disease (ILD) have previously been reported in patients being treated with erlotinib, however, several confounding factors exist such as prior radiotherapy, prior chemotherapy, pulmonary infections, and metastatic lung disease.

2.5.2. Conclusions on clinical safety

The safety of erlotinib in the subgroup of patients with EGRF activating mutation in the SATURN study is as expected. There are no new safety findings. There were no new safety findings in the IUNO study.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.5.4. Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on the revised indication and the results that have led to the conclusion that erlotinib is no longer indicated for maintenance treatment in patients without an epidermal growth factor receptor (EGFR) activating mutation.

The DHPC is provided in Attachment 3 together with the communication plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent by 14 January 2016 to healthcare providers.

2.6. Risk management plan

The MAH did not provide an updated RMP. A justification for non-inclusion of the updated Risk Management Plan was provided. Since there has been insufficient time to finalise the RMP update between release of the IUNO data and submission of this application, and in view of the urgency to amend the Product Information, the MAH commits to update and submit the Risk Management Plan (RMP) as soon as possible via a separate variation application. This has been considered an acceptable approach by the CHMP.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- changes to the PL were considered not affecting readability.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits of erlotinib in terms of long-term outcome in patients with NSCLC with EGFR activating mutation have been demonstrated in several clinical trials. A subgroups analysis in the SATURN study has shown a remarkable gain in median PFS in this patient population in the switch maintenance setting after first-line therapy. The updated results of the study were consistent with the earlier results and confirm the clinically relevant effect of erlotinib in patients with activating EGRF mutations. The findings in the SATURN study in the subgroup of patients with EGFR activating mutation are supported by the ATLAS study, a meta-analysis by Lui et al (2015) and by a pooled analysis by Paz-Ares et al. (2014). No effect on OS and PFS was shown in the IUNO study in patient which did not harbour EGFR activating mutations. Overall, these data supporting the change in the indication to restrict to patients with locally advance NSCLC with EGFR activating mutations and stable disease after first line treatment.

Uncertainty in the knowledge about the beneficial effects

The data to support the indication is mainly based on one study, the SATURN study, where EGFR activating mutations were pre-specified and were used as a stratification factor. The meta-analysis by Lui et al. included three studies in the maintenance setting, where EGFR-TKIs were compared with placebo. The pooled analysis showed a statistically significant HR, but the results seems to be mainly driven by the SATURN study. In addition, the supportive study, the Paz-Ares study, while providing evidence for the efficacy of EGFR-TKI's in first-line and other lines of therapy, did not provide any direct evidence for the use of erlotinib in maintenance setting. Given these caveats, the data from the SATURN study and the supportive evidence in the literature are considered robust enough to support the change in indication.

It was noted that at the time of the submission of this application, the final CSR for IUNO had not yet been finalised. Therefore the MAH has agreed to submit the final CSR for the IUNO study post approval, and also committed to submit a variation in order to update the RMP at the earliest convenience.

Risks

Unfavourable effects

The safety profile of patients with EGFR activating mutation is in line with the findings for the entire population in the SATURN study. Although the number of patients is low, no concerns have been raised and no differences were observed. The most common AEs were skin disorders (rash) and diarrhea. These are well-known AEs related to the use of erlotinib and are clinically manageable. There are no major differences with regard to the number of deaths. Only one SAE (left ventricular dysfunction) occurred in the erlotinib arm and none in the placebo arm. The event resolved with following treatment.

With regard to the IUNO, the most common AEs in the erlotinib arm were rash, diarrhea, dyspnea and cough. The above pattern in AEs are in line with the known safety profile of erlotinib in patients with NSCLC.

Uncertainty in the knowledge about the unfavourable effects

No new safety signals have been detected and the adverse event profile is well-known for erlotinib as for other EGFR-TKI's. The safety of erlotinib should be viewed in the context of that this patient population in general have a very poor prognosis.

Effects Table

Table 7: Effects table for erlotinib in the maintenance setting in patients with EGFR activating mutations and stable disease

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Progression-free survival	Months	44.6	13.0	HR = 0.10 (95%CI; 0.04, 0.25), p<0.0001	
Unfavourable Effects						
Diarrhoea		N (%)	8/22 (36.4%)	3/29 (11.5%)	Well-known AE related to erlotinib. Clinically manageable.	
Rash		N (%)	10/22 (45.5%)	1/20 (3.8%)	Well-known AE that is correlated with the effect of erlotinib.	

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The remarkable gain in median PFS in the subgroup of patients with EGFR activating mutation in the SATURN study is clinically relevant, considering the poor prognosis that these patients are otherwise faced with. There is a clear biological and molecular rational for the treatment effect. The safety profile of erlotinib is well-known and well-characterised. The majority of AEs related to erlotinib are clinically manageable and pose no major concerns.

Benefit-risk balance

The benefit-risk balance of erlotinib in the indication "Tarceva is indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy. " is considered positive in patients with EGFR activating mutations being treated in the switch maintenance setting.

Discussion on the Benefit-Risk Balance

The remarkable effect seen in median PFS is not translated to an OS gain in the SATURN study. The use of erlotinib as maintenance after first line treatment shows no detrimental effect on OS in the subgroup of patients with EGFR activating mutations. The KM curves are overlapping. This is somewhat expected, as any effect of erlotinib on OS is bound to be diluted by cross-over and later lines of therapy.

Based on the SATURN study, switch maintenance treatment was deemed justified in patients with stable disease after first-line treatment. Recent scientific publications (eg the ATLAS study, meta analyses on the effect of EGFR-TKIs) provided further support for the findings in the SATURN study in this subpopulation.

In conclusion, in the context of the totality of the efficacy and safety data presented, the benefits associated with clinically relevant effects in terms of PFS and OS outweigh the risks with regard to the use of erlotinib in the switch maintenance setting in patients with stable disease after first-line treatment with EGFR

activating mutations. In light of the results from the IUNO study and other available information on erlotinib, the MAH is recommended to discuss the use of erlotinib for the treatment of patients without EGFR activating mutation status with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Modification of the indication to limit maintenance treatment to NSCLC patients with an EGFR-activating mutation and stable disease after first-line chemotherapy based on the data from study BO25460 (IUNO). Consequently, SmPC sections 4.1, 4.8 and 5.1 have been updated. The Package leaflet is updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

This CHMP recommendation is subject to the following amended condition:

Conditions and requirements of the marketing authorisation

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

An updated RMP shall be submitted by March 2016.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Modification of the indication to limit maintenance treatment to NSCLC patients with an EGFR-activating mutation and stable disease after first-line chemotherapy based on the data from study BO25460 (IUNO). Consequently, SmPC sections 4.1, 4.8 and 5.1 have been updated. The Package leaflet is updated accordingly.

Summary

Please refer to the Scientific Discussion Tarceva-II-43.

References

[1] Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: Randomized, double-blind, placebo-controlled, phase IIIb trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non–small-cell lung cancer. J Clin Oncol. 2013;31(31):3926-34.

[2] Liu J, Sheng Z, Zhang Y, et al. The efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for molecularly selected patients with non-small cell lung cancer: A meta-analysis of 30 randomized controlled trials. Targ Oncol. 2015 (Epub ahead of print); doi 10.1007/s11523-015-0376-7.

[3] Paz-Ares L, Soulières D, Moecks J, et al. Pooled analysis of clinical outcome for EGFR TKI treated patients with EGFR mutation-positive NSCLC. J Cell Mol Med. 2014;18(8):1519-39.