9 November 2017
EMA/184796/2018
Committee for Medicinal Products for Human use (CHMP)

Assessment report

Tarceva

International non-proprietary name: erlotinib

Procedure No. EMEA/H/C/000618/II/0051

Marketing authorisation holder (MAH): Roche Registration Limited

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Rapporteur(s) and type of application	
CHMP Rapporteur:	Sinan B. Sarac
PRAC Rapporteur:	N/A
This application is in the area of:	(Non-)Clinical
eCTD sequences related to the procedure:	0087
☒	The relevant sections of this Assessment Report were endorsed by the PRAC

Contact information	
Contact person – CHMP Rapporteur	Name: Kristina Bech Jensen Email: krb@dkma.dk
Assessor – CHMP Rapporteur	Name: Sinan B. Sarac Email: krb@dkma.dk
Contact person - PRAC Rapporteur	NA
Assessor – PRAC Rapporteur	NA
EMA Procedure Manager	Name: Biljana Simpraga Tel: +44 20 36607912 Email: biljana.simpraga@ema.europa.eu
EMA Procedure Assistant	Name: Katerina Kaprini Tel: +44 20 36607230 Email: Katerina.Kaprini@ema.europa.eu

Declarations

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Assessment Timetable/Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	17 April 2017	17 April 2017
CHMP Rapporteur Assessment Report	22 May 2017	22 May 2017
CHMP members comments	6 June 2017	6 June 2017
Updated CHMP Rapporteur Assessment Report	8 June 2017	n/a
Start of written procedure	13 June 2017	13 June 2017
Request for Supplementary Information	15 June 2017	15 June 2017
Submission:	08 September 2017	06 September 2017
Procedure re-start:	11 September 2017	11 September 2017
CHMP Rapporteur Assessment Report	16 October 2017	13 October 2017
CHMP members comments	30 October 2017	30 October 2017
Updated CHMP Rapporteur Assessment Report	03 November 2017	n/a
Opinion	09 November 2017	09 November 2017

Table of contents

1. Background information on the procedure 6
1.1. Requested type II variation 6
1.2. Rationale for the proposed change 6

2. Overall conclusion and impact on the benefit/risk balance 6

3. Recommendations 8

4. Scientific discussion 9
4.1. Introduction 9
4.1.1. Rationale for inhibition of EGFR by Erlotinib 10
4.2. Clinical Efficacy aspects 12
4.2.1. Subgroup analyses in NSCLC patients with EGFRwt tumours 12
4.2.2. Efficacy of erlotinib in second line treatment of NSCLC patients clinically selected for EGFR wild type (squamous NSCLC) 16
4.2.3. Discussion 53
4.3. Clinical Safety aspects 55

5. Request for supplementary information 56

6. Assessment of the responses to the request for supplementary information 57

7. Attachments 84

List of abbreviations

AE	adverse event
ARMS	amplification refractory mutation system
BSC	best supportive care
CI	confidence interval
CPHG	Collège des Pneumologues des Hôpitaux Généraux
CR	complete response
CSR	clinical study report
CT	computerized tomography
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30
EORTC-QLQ-LC13	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Lung Cancer Module
FACT-L	Functional Assessment of Cancer Therapy - Lung
FISH	fluorescence in situ hybridization
HR	hazard ratio
IQR	interquartile range
ITT	intent-to-treat
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MRI	magnetic resonance imaging
NCCN	National Clinical Cancer Network
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PCR-RFLP	PCR based restriction landmark fragment polymorphism
PFS	progression-free survival
PR	partial response
QoL	quality of life
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RR	risk ratio
SCE	Summary of Clinical Efficacy
SD	stable disease
TKI	tyrosine kinase inhibitor
TNM	tumor-node-metastasis
TTP	time to progression
2L	second-line
3L	third-line

1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 30 March 2017 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the Real World Data Reports (BIOMARQUEURS FRANCE CSR and ESCAP-2011-CPHG CSR), a literature review and a new CSR Addendum of the previously submitted pivotal study BR.21, in order to discuss the currently available evidence supporting the use of erlotinib for treatment of patients with locally advanced or metastatic NSCLC without EGFR-activating mutations after failure of at least one prior chemotherapy regimen, as requested in a recommendation originating from variation EMEA/H/C/000618/II/0043.

The requested variation proposed no amendments to the Product Information.

1.2. Rationale for the proposed change

The MAH submitted this Type II variation in order to address the following recommendation originating from variation II/43:

In light of the results from the IUNO study and other available information on erlotinib, it is recommended that the MAH 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.

No changes to the PI or to the RMP were initially proposed by the MAH.

2. Overall conclusion and impact on the benefit/risk balance

The IUNO study, which has been assessed in a previous variation, showed no benefit of early erlotinib treatment in patients with NSCLC without known EGFR activating mutations compared to placebo. In response to this IUNO study, the FDA decided to limit both the early switch-maintenance indication and the second line treatment indication. In the EU, the IUNO study led to the revision of the maintenance indication and the benefit/risk balance in the second-line came into question, in particular for the patients without an EGFR mutation. This question led to the recommendation which gave rise to the current submission in which the MAH discussed the currently available evidence supporting the use

of erlotinib as second-line and further treatment in patients with locally advanced or metastatic NSCLC with WT-EGFR. This data has been provided in the first round.

With the responses to the Request for Supplementary Information (RSI), the MAH was asked to provide additional discussion on the clinical evidence in order to support activity of erlotinib (and therefore a positive benefit/risk balance of erlotinib) as second and beyond line of treatment of NSCLC patients with EGFR WT status. In the discussion the MAH was asked to include the concerns on the interpretability of the presented data, the patient population that is likely to benefit and the rationale that EGFR signalling must the able to drive tumour growth in WT EGFR NSCLC.

Interpretability of the presented (pre-) clinical evidence

The subgroup analysis in WT EGFR patients of the BR.21 study is discussed in the initial application. However, the interpretability of the data is hampered by the limited sample size and the fact that analyses have been performed post-hoc. The applicant agrees that these data "could be challenged in view of the retrospective nature and the small sample size". However, the MAH indicates that the presented data in the answer consistently support the conclusion of a modest but clinically relevant benefit of erlotinib in patients with WT EGFR NSCLC.

The pre-clinical data presented are not considered sufficient. In the presented literature no clear distinction is made between EGFR and WT-EGFR. At the time that the presented literature was published, the activating mutations were not described yet and specific testing for these mutations was not yet common practice. Therefore, these publications do not provide the evidence specifically for WT-EGFR signalling, while needed for the purpose of this PAM. Furthermore, no additional/new information was provided in the discussion on the concerns raised for the subgroup analyses of the BR.21 study performed in NSCLC patients with EGFR WT status and/or with squamous histology. Therefore, the interpretability of the data on the efficacy of erlotinib compared to placebo is still hampered by the limited sample size, the fact that analyses have been performed post-hoc and the possibility for false positives.

The presented data still consist of a highly heterogeneous group of publications related to several studies performed in different populations, and/or in different treatment setting and/or employing different comparators. The interpretation of the results is hampered in several studies due to the limited sample size and the fact that EGFR WT patients represented only subgroups of the population treated in the study. Overall, conflicting results are presented in the literature, ranging from studies (e.g., TAILOR) clearly indicating superiority of chemotherapy vs erlotinib in terms of PFS and OS in EGFR WT patients and other trials/subgroup analyses suggesting no significant difference in OS when comparing chemotherapy to erlotinib (for the TITAN, DELTA and PROSE trial). To be noted, a numerical trend in median PFS favouring chemotherapy was identified in all these trials.

In response to CHMP adopted RSI, the MAH provided new data by means of two case studies. Both case studies point towards an effect of erlotinib in WT-EGFR patients. However, two case studies do not provide reliable enough evidence for erlotinib to be effective over chemotherapy in the WT-EGFR NSCLC population.

In conclusion, the concerns on the interpretability of the clinical evidence to support the use of erlotinib in WT-EGFR NSLCLC currently presented (by e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests) persist and therefore the clinical efficacy of erlotinib in second- and further-line WT EGFR NSCLC remains unclear.

The rationale that EGFR signalling is the able to drive tumour growth in WT EGFR NSCLC

It has been known for a long time that EGFR signalling is able to activate pathways related to tumour growth. Based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

Conclusion

The IUNO study, which has been assessed in a previous variation, showed no benefit of early erlotinib treatment in patients with NSCLC without known EGFR activating mutations. In the EU, the IUNO study led to the revision of the maintenance indication and the benefit/risk balance in the second-line indication after failure of prior chemotherapy came into question, in particular for the patients without an EGFR mutation.

The benefit/risk balance of erlotinib in the 2nd-line and later treatment of patients with locally advanced or metastatic WT-EGFR NSCLC involves uncertainties for the following reasons:

First, the concerns persist on the interpretability of the currently presented clinical evidence to support erlotinib efficacy in comparison to both placebo as chemotherapy in WT-EGFR NSLCLC (e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests).

Second, it has been known for a long time that EGFR signalling is able to activate pathways related to tumour growth, however, based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

As a consequence, the MAH has proposed to reflect the uncertainties in relation to the 2nd-line and beyond NSCLC indication including the following wording in section 4.1 of the SmPC:

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated when other treatment options are not considered suitable.

The CHMP agrees to this revision of the indication.

Scientific Summary for the EPAR:

Tarceva is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated when other treatment options are not considered suitable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	I

Update of section 4.1 of the SmPC in relation to the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen based on a review of relevant literature, Real World Data Reports (BIOMARQUEURS FRANCE CSR and ESCAP-2011-CPHG CSR) and a new CSR Addendum of the previously submitted relevant pivotal study BR.21, as requested by the CHMP following assessment of variation EMEA/H/C/000618/II/0043

☒ is recommended for approval.

The variation leads to amendments to the Summary of Product Characteristics.

4. Scientific discussion

4.1. Introduction

Erlotinib was first approved in the European Union (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. Approval was based on the results of **BR.21**, a 2:1 randomized, double-blind, placebo-controlled Phase 3 study of erlotinib (150 mg daily) for second- or third line therapy of advanced NSCLC.

By 2016, the following NSCLC indications had been approved for erlotinib in the EU:

- *First-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations.*
- *Switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.*
- *Treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.*

On 17 December 2015, CHMP granted a positive opinion (with Commission Decision in January 2016) for the modification of the maintenance indication to limit treatment to NSCLC patients with an EGFR-activating mutation based on the data from the IUNO (BO25460) maintenance study (variation EMEA/H/C/000618/II/0043). The results of IUNO study failed to show a benefit for the maintenance treatment of patients with NSCLC without EGFR activating mutations. Treatment with first line chemotherapy + maintenance erlotinib + second line chemotherapy was not superior to treatment with first line chemotherapy + maintenance placebo + second line erlotinib with a clear lack of benefit in terms of progression-free survival (PFS) for erlotinib versus placebo in the maintenance phase.

Within the above variation EMEA/H/C/000618/II/0043, the Marketing Authorization Holder (MAH) agreed to address and implement the following Post-authorisation measure/ Recommendation:

"In light of the results from the IUNO study and other available information on erlotinib, it is recommended that the MAH discuss the use 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."

In October 2016, the MAH met with the European Medicines Agency (EMA) and Rapporteurs to present the company position on the use of erlotinib for the treatment of patients with locally advanced or

metastatic NSCLC without EGFR-activating mutations after failure of at least one prior chemotherapy regimen, and to discuss the most appropriate procedure to fully address the recommendation. Agreement was reached to submit a Type II variation.

Therefore, the purpose of this Type II variation is to discuss the currently available evidence supporting the use of erlotinib for treatment of patients with locally advanced or metastatic NSCLC without EGFR-activating mutations after failure of at least one prior chemotherapy regimen.

4.1.1. Rationale for inhibition of EGFR by Erlotinib

4.1.1.1. Differential inhibitory activity of erlotinib for mutant EGFR and Wilde-Type (WT) EGFR

Erlotinib acts via direct, selective (only the EGFR tyrosine kinase) and reversible inhibition of the human EGFR tyrosine kinase. While differential sensitivity for WT EGFR and mutant EGFR is observed for erlotinib, clear activity has been shown in pre-clinical studies in both settings. However, kinetic assays revealed that both mutants exhibit a higher binding constant for ATP, relative to the WT EGFR. The Inhibitory constant for WT EGFR was 17.5 nmol/L, while it was 6.3 nmol/L for the L858R mutation and 3.3 nmol/L for the del(746-750) in exon 19. This greater sensitivity of mutant EGFR was confirmed in both an in vitro cell line model as an in vivo mouse model.

CHMP comment:

Carey et al. indeed showed that erlotinib is capable of inhibiting WT EGFR in non-clinical models. The inhibitory constant is much lower in the mutants indicating that more erlotinib is required to inhibit WT EGFR (confirmed in the in vitro and in vivo studies). For example, in mice WT EGFR tumours react with 150 mg/kg/d (max tolerated dose), while mutant EGFR tumours react on 12 mg/kg/d or 50 mg/kg/d.

Erlotinib is a relatively selective reversible EGFR tyrosine kinase inhibitor. From a mechanistic point of view activity of the drug is expected in situations where prolonged activation of the EGFR receptor triggers tumour oncogenic activity through proliferation, invasion and metastasis, as it is the case of NSCLC patients harbouring EGFR activating mutations. In EGFR WT tumours, where there is no constitutive activation of the EGFR signalling, activity of erlotinib is different from a theoretical point of view.

The rationale supporting activity of Erlotinib in EGFR WT tumours is that EGFR signalling is able to drive tumour growth in the WT EGFR NSCLC. However, based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

Although both first-generation TKIs erlotinib and gefitinib target EGFR, only erlotinib has been shown to be effective in patients with WT EGFR tumours. There are a number of reasons to explain this difference:

1. Gefitinib reaches much lower plasm expression levels than erlotinib after administration (while higher dose is required to inhibit WT EGFR).
2. The metabolite of erlotinib retains most of its activity, while the metabolite of gefitinib does not.
3. Erlotinib might inhibit the IPP complex and consequent EMT, while gefitinib does not.
   Explanation: A proteomics study revealed binding of erlotinib to the integrin-linked kinase (ILK), α-parvin and PINCH complex (IPP complex). This complex is involved in the epithelial-

to-mesenchymal transition (EMT), the process by which epithelial cells lose adhesion molecules and acquire a mesenchymal phenotype allowing them to migrate into the stroma and become invasive. Erlotinib sensitivity has been correlated with EMT status (both in vitro and in vivo) and erlotinib has been shown to reverse the EMT phenotype in inflammatory breast cancer cells.

CHMP comment:

Though interesting from a scientific point of view, no (non-)clinical data are presented to justify the idea of Erlotinib inhibiting the IPP complex and EMT. The MAH should discuss the available clinical data to confirm the hypothesis of Erlotinib inhibiting the IPP complex.

4.1.1.2. Differential sensitivity of Erlotinib for chemo-resistant and chemo-sensitive tumours

Preclinical studies suggest that possibility that there are differences in the characteristic of tumours that have responded or stabilized following first line chemotherapy compared with those that are refractory to or have relapsed on first-line therapy. Results showed that in some of the chemo-resistant tumour cell lines acquired resistance to cytotoxic agents was associated with an increased EGFR expression and increased sensitivity to erlotinib compared with the respective parental tumour cell line. This increased EGFR expression and sensitivity might have clinical consequences in that EGFR TKIs may be more effective in patients with certain types of chemo-refractory tumours than in patients with the corresponding chemo-naïve tumours.

Taking these findings into account, it is plausible that patients who have disease control or response to first-line chemotherapy and who are treated with erlotinib (maintenance indication, IUNO study) may not have an incremental benefit to such a treatment switch while patients who are treated with erlotinib after failure of first-line chemotherapy and progression of disease (second-line, BR.21 study) could have different tumour characters and consequently a different response to erlotinib. Therefore, the maintenance phase efficacy results of the IUNO (BO25460) study should not be extrapolated to the second-line treatment setting

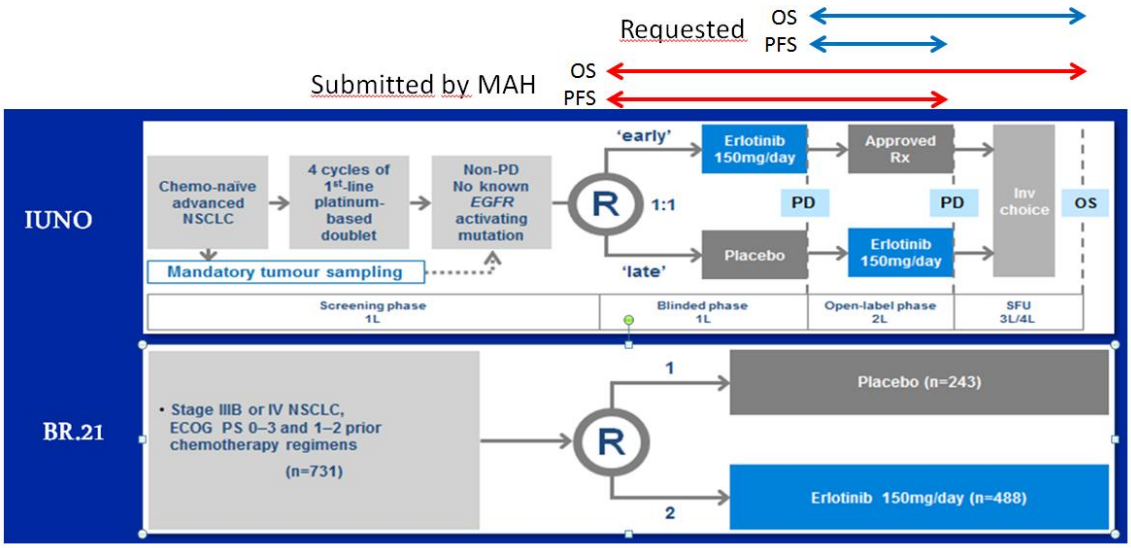
In the IUNO study, patients who had progressive disease during the maintenance phase were treated in the second line with erlotinib or chemotherapy. Interpretation of these treatments is challenging as this part of the study was not randomized and the study was not designed to assess the impact on OS of chemotherapy versus erlotinib as second line treatment. However, if erlotinib was not efficacious in the second line setting, one may have expected to see an trend for improved OS in the arm containing second line chemotherapy. This is not evident with median OS values of 9.46 months in the second-line erlotinib and 9.72 months in the arm containing second line chemotherapy.

CHMP comment:

It is hypothesized by the MAH that the difference between chemo-sensitive and chemo-resistant is mainly based on the EGFR expression (which is higher in resistant cells). The IUNO study only included patients with "high" EGFR expression levels (>10% of the tumour cells showing membrane staining with IHC). Despite this inclusion criterium, the early switch maintenance therapy with erlotinib did not result in a better efficacy than with placebo. Therefore, "high" EGFR expression due to chemo-resistance cannot be the only reason for Erlotinib showing a benefit in second- and further-line treatment in EGFR WT NSCLC. The MAH should comment on this observed discrepancy.

The MAH suggests that no big difference can be detected between the OS of the second-line erlotinib and the second-line chemo in the IUNO study. This OS is calculated with the starting point at randomization (Figure 1: red arrows). The MAH is requested to provide the PFS and OS with a starting point at first time PD (Figure 1: blue arrows), to remove the potential effect of the maintenance treatment period (PFS2 and OS2).

Figure 1: Study set up IUNO and BR.21 studies.



4.2. Clinical Efficacy aspects

4.2.1. Subgroup analyses in NSCLC patients with EGFRwt tumours

Retrospective testing for EGFR mutations on tissue samples from this study was performed by the MAH in 2008. After histologic evaluation, tumour samples from 233/328 patients with available samples (32% of the enrolled population) were considered to be adequate for EGFR mutation analyses. Two assays capable of detecting EGFR mutations in DNA samples containing 5% to 10% tumour were used. An allele specific polymerase chain reaction (PCR) test - the Amplified Refractory Mutation System [Whitcombe et al. 1999] - was performed using the ScorpionsIM Kit (DxS, Manchester, United Kingdom) for detection of exon 19 (E746_A750del) deletions and exon 21 (L858R) mutations. This test uses multiple sets of allele specific primers, each of which is labeled with fluorescent dye specific to each target allele. PCR amplification yields different levels of fluorescence in wavelengths that correspond to the relative concentration of target alleles in the sample DNA. The test was a commercially available Laboratory Developed Test (LDT) which was subsequently marketed as the therascreen® EGFR PCR Kit following acquisition of DxS Ltd. by Qiagen in 2009. The limit of detection claimed by the manufacturer at the time was 1% mutant DNA in a background of wild-type DNA. An updated version of the test is currently marketed as the therascreen® EGFR RGQ PCR Kit using the same methods for detection of EGFR mutations as the original test. The limits of detection for this test for the different EGFR mutations range from 0.5% to 7.0% [therascreen® EGFR RGQ PCR Kit Handbook]. The clinically validated cobas® EGFR Mutation Test v1 is based on similar technology and can reliably detect mutant EGFR down to ~5% sensitivity.

The second, confirmatory analysis of EGFR mutations in tumor samples from patients in the BR.21 study was performed using an orthogonal method that differentiates fluorescent PCR fragments on the basis of size by capillary electrophoresis for exon 19 deletions [Pan et al. 2005]. For exon 21 mutations (L858R), a PCR based restriction fragment length polymorphism (PCR-RFLP) method was used, which takes advantage of the fact that the mutation of T>G at base 2573 of the EGFR cDNA creates a new restriction site for the enzyme Sau961. Thus, when the L858R mutation is present, the enzyme cleaves the PCR product whereas when the PCR product is wild-type no cleavage occurs. There is no clinically validated commercial version of this assay although the literature suggests that this assay can readily detect the exon 19 deletion in the presence of 6% DNA and the exon 21 L858R mutation in the presence of 3% DNA [Pan et al. 2005].

CHMP comment:

Although both types of mutational analysis used by the MAH are not clinically validated, they are considered to be sensitive and require a low amount of tumour DNA. This reduces the chance of acquiring false negative results. Nevertheless, several questions remain on the analysed samples. Only 233 of 328 were considered to be adequate for EGFR mutation analysis, of which in the end 204 could be tested for a EGFR mutation. As the criteria for a sample to be adequate (for example, EGFR expression, tumour DNA content, preservation method?) might introduce selection bias in the WT-EGFR population.

- the MAH is asked to elaborate on the criteria used to categorize a sample as adequate and to indicate why for 29 samples no proper mutational analysis was obtained.

-The MAH should also present the EGFR expression level (as assessed by IHC) of patients with proper samples for mutational analysis.

Mutational analysis of EGFR was successful in 204/233 patients with adequate tumor samples. Two efficacy analyses were performed by the MAH in 2008 and 2013 (using the clinical study report [CSR] data cut-off date of 30 January 2004).

In the first sponsor analysis, reported by Zhu et al. [2008], the focus was on exon 19 deletions and exon 21 L858R mutations. The EGFR wild-type subgroup (n = 170; 115 in the erlotinib arm and 55 in the placebo arm) was not an exclusive wild-type subgroup but consisted of patients whose tumours were EGFR wild-type and also patients whose tumours had other indeterminate variants in EGFR.

The second, more conservative analysis conducted by the MAH focused on the EGFR wild-type subgroup and comprised 150 patients (102 in the erlotinib arm and 48 in the placebo arm). The analysis excluded patients whose tumours had exon 19 deletions and exon 21 L858R mutations, as well as patients whose tumours had other indeterminate variants in EGFR. Because the number of patients with known EGFR mutation status was small, as tissue samples from less than half of the study participants were available for testing, a powered analysis with significant findings could not be expected. Nonetheless, the HRs for PFS and OS of the EGFR wild-type subgroup were similar to the full analysis set (FAS) population. The analysis showed a numerically favourable OS in the EGFR wild-type subgroup with an unadjusted HR of 0.75 (95% CI: 0.52, 1.10; p = 0.1443) in favour of erlotinib, which was similar to the magnitude in the full analysis set (unadjusted HR = 0.76 [95% CI: 0.64, 0.91]; p = 0.0018). A PFS benefit (unadjusted HR = 0.56; 95% CI: 0.39, 0.81; p = 0.0013) was observed for erlotinib compared with placebo in the EGFR wild-type subgroup, which was consistent with that seen in the FAS population (unadjusted HR = 0.64; 95% CI: 0.54, 0.75; p<0.0001) ((Table 1). Regarding response rate, the EGFR wild-type subgroup demonstrated a higher response rate in erlotinib-treated patients (5.9% [95% CI: 2.2, 12.4]) compared with placebo-treated patients (2.1% [95% CI: 0.1, 11.1%]) and the response rate was consistent with that observed in the erlotinib arm of the FAS

(8.0% [95% CI: 5.7, 10.8%]). Thus, these data from BR.21 are supportive of the clinical benefit of erlotinib over placebo in EGFR wild-type patients in the second/further line settings.

Table 1 BR.21 Summary of Efficacy Results for NSCLC Patients

	Treatment Group (n)	Median (Mo.) [95% CI]	Hazard Ratio [95% CI]	p-value (Log-Rank Test)
Overall Survival				
ITT (n = 731)	Erlotinib (488)	6.7 [5.5, 7.8]	0.76	
	Placebo (243)	4.7 [4.1, 6.3]	[0.64, 0.91]	0.0018
EGFR WT (n = 150)	Erlotinib (102)	8.1 [5.8, 10.9]	0.75	
	Placebo (48)	3.4 [2.5, 6.8]	[0.52, 1.10]	0.1443
EGFRmut+ve (n = 34)*	Erlotinib (15)	10.9 [3.9, NE]	0.55	
	Placebo (19)	8.3 [3.3, 11.1]	[0.25, 1.19]	0.1217
Progression-Free Survival				
ITT (n = 731)	Erlotinib (488)	2.2 [1.9, 2.9]	0.64	
	Placebo (243)	1.8 [1.8, 1.9]	[0.54, 0.75]	< 0.0001
EGFR WT (n = 150)	Erlotinib (102)	2.2 [2.0, 4.0]	0.56	
	Placebo (48)	1.8 [1.6, 1.9]	[0.39, 0.81]	0.0013
EGFRmut+ve (n = 34)*	Erlotinib (15)	5.6 [1.5, 9.0]	0.48	0.0414
	Placebo (19)	1.8 [1.6, 1.9]	[0.23, 1.00]	
Response Rates				
		Response Rate [a] (CR + PR) [95% CI] [b]	**Difference in Response Rate [95% CI] [c]**	**P Value (CMH Test)**
ITT (n = 731)	Erlotinib (488)	39 (8.0%) [5.7, 10.8]	7.17	
	Placebo (243)	2 (0.8%) [0.1, 2.9]	[4.3, 10.0]	< 0.0001
EGFR WT (n = 150)	Erlotinib (102)	6 (5.9%) [2.2, 12.4]	3.80	
	Placebo (48)	1 (2.1%) [0.1, 11.1]	[−3.4, 11.0]	0.3051
EGFRmut+ve (n = 34)*	Erlotinib (15)	4 (26.7%) [7.8, 55.1]	26.67	
	Placebo (19)	0 (0.0%) [0.0, 17.6]	[0.2, 53.2]	0.0182

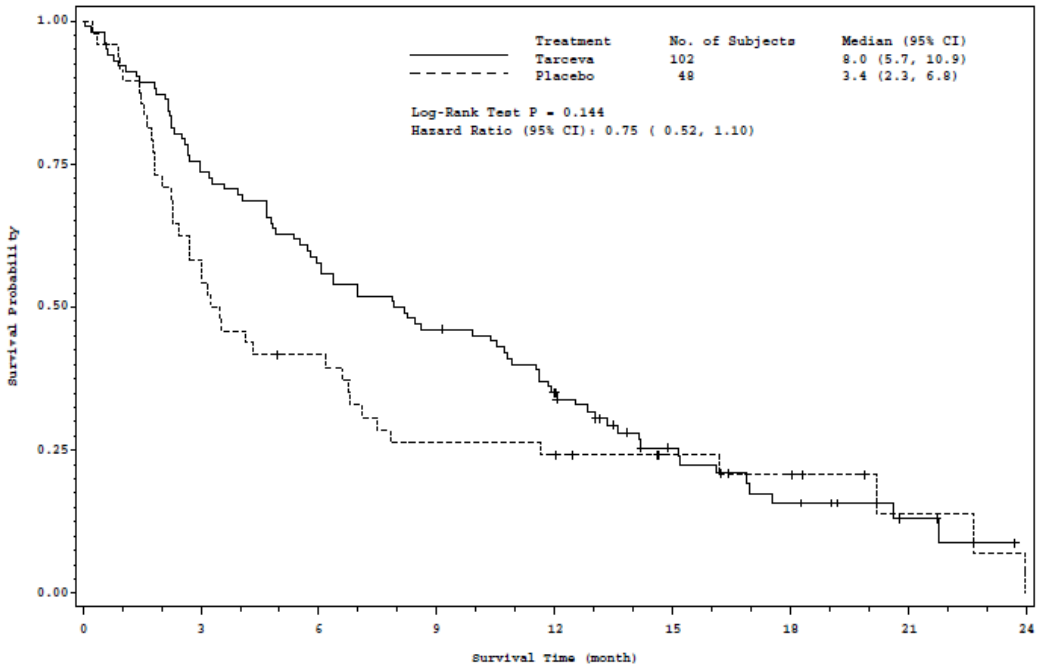
CMH = Cochran-Mantel-Haenszel; CI = confidence interval; CR = complete response; EGFR = epidermal growth factor receptor; ITT = intent to treat; Mo. = months; mut+ve = mutation positive; NE = not estimated; NSCLC = non-small cell lung cancer; PD = disease progression; PR = partial response; SD = stable disease; WT = wild-type.
Hazard ratio < 1 is in favor of erlotinib. Cut-off Date: 30 January 2004.
[a] Best overall response of confirmed CR or PR; nonresponder is SD, PD, or missing.
[b] 95% CI for one sample binomial using Pearson-Clopper method.
[c] Approximate 95% CI for difference of two rates using Hauck-Anderson method.

* Exon 19 deletion mutation or exon 21 L858R substitution mutation.

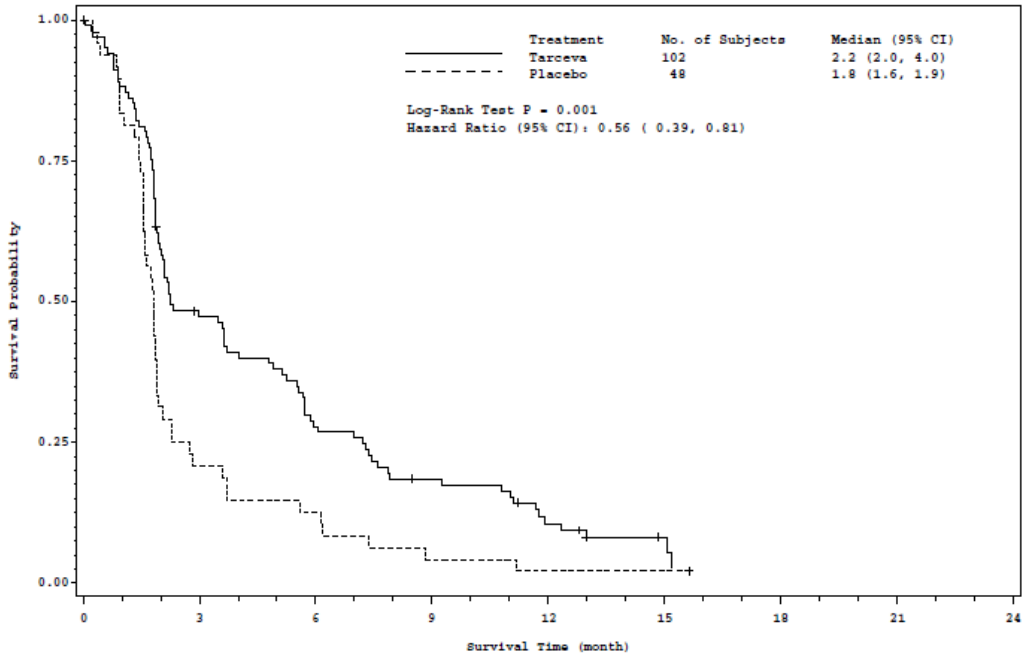
Source: BR.21 Addendum source outputs

Figure 1Kaplan-Meier curves of OS (upper panel) and PFS (lower panel) in NSCLC patients with EGFR wild-type tumors in the BR.21 study

OS



PFS



Source: Module 2.7.3 Figure 1

CHMP comment

The MAH performed two analyses on the BR.21 study. The second analysis excluded patients with exon 19 del and exon 21 L858R mutations AND other indeterminate variants. Thus, this second analysis was more conservative than the first analysis. The analysis of OS shows HR = 0.75 (p = 0.1443), which was in line with the HR for the ITT population (HR = 0.76, p = 0.0018). The HR in the EGRF mutated was 0.55 (p = 0.1217).

The MAH is asked to provide data on EGFR expression level of the samples with known EGFR mutation status, as the increased efficacy in the WT group might be related to an increased EGFR expression status. Please provide also the efficacy parameters for patients with low and high expression level in both the WT and mutant EGR subgroups. Furthermore, it should be noted that in the subgroup analysis presented in patients with EGFR WT tumours enrolled in the BR.21 study, the difference in median PFS observed between the two study arms, although statistically significant, is of very modest clinical relevance (2.2 vs 1.8 months with erlotinib and placebo, respectively).

4.2.2. Efficacy of erlotinib in second line treatment of NSCLC patients clinically selected for EGFR wild type (squamous NSCLC)

The reported incidence of EGFR mutations in patients with squamous cell carcinoma has been reported to be 2.7% [Forbes et al. 2008]. However, the true incidence in pure squamous NSCLC may be much lower [Rekhtman et al. 2012]. This level of EGFR mutation incidence is low enough for the National Clinical Cancer Network (NCCN) to not recommend routine EGFR testing in this population unless they have never smoked, if only a small biopsy specimen (i.e. not a surgical resection) was used to assess histology, or if the histology is mixed [NCCN Guidelines, 2017]. Consequently, NSCLC patients with squamous cell histology subtype can be considered a clinically selected surrogate for the NSCLC EGFR wild-type population.

Subgroup analysis from the BR.21 study

In the BR.21 study, patients with squamous cell histology comprised 30% (144/488) of patients in the erlotinib treatment arm and 32% (78/243) of patients in the placebo arm. An overview of the demographic characteristics of the squamous cell subpopulation is shown in

Table 1. Demographics were generally consistent with the overall BR.21 population, although as expected for a population of patients with squamous cell carcinoma, the relative percentage of male patients compared to female patients was higher than for the overall BR.21 population.

Pre-specified subgroup analyses based on the stratification factors at randomization and baseline were performed and reported in the original BR.21 CSR. These stratification factors (including histology type) were examined in exploratory univariate analyses to assess the robustness of the overall survival and progression free survival results.

Results showed that among patients with squamous cell histology (144 erlotinib; 78 placebo), the median survival of patients who received erlotinib (5.57 months; 95% CI 4.67, 7.00) was longer than in the placebo group (3.58 months; 95% CI 3.15, 4.34) with non-overlapping confidence intervals. The HR of 0.67 (95% CI 0.50, 0.90) was similar to that observed in both the ITT analysis for overall survival reported in the BR.21 CSR (HR = 0.76; 95% CI 0.64, 0.91) (Section 11.4.1.1 of BR.21 CSR) and the retrospective exploratory subgroup analysis of OS in EGFR wild-type patients conducted by the MAH.

Median PFS for squamous patients receiving erlotinib was 9.86 weeks (95% CI 8.57, 15.14) compared with 7.86 weeks (95% CI 7.43, 8.14) for patients receiving placebo. The HR of 0.53 (95% CI 0.39, 0.70) was consistent both with the value observed in the ITT analysis for PFS (HR = 0.64; 95% CI 0.54, 0.75) (Section 11.4.1.6 of BR.21 CSR) and with the retrospective exploratory subgroup analysis of PFS in EGFR wild-type patients.

Table 1 Demographic data for the subgroup of NSCLC patients with squamous cell histology in the BR.21 study

Parameter	Erlotinib N = 144	Placebo N = 78
Gender		
Male	114 (79.2%)	64 (82.1%)
Female	30 (20.8%)	14 (17.9%)
Race		
White	119 (82.6%)	64 (82.1%)
Black	6 (4.2%)	5 (6.4%)
Oriental	14 (9.7%)	7 (9.0%)
Other	5 (3.5%)	2 (2.6%)
Age (years)		
18-39	2 (1.4%)	0
40-64	83 (57.6%)	42 (53.8%)
≥ 65	59 (41.0%)	36 (46.2%)
ECOG PS		
0	16 (11.1%)	6 (7.7%)
1	59 (41.0%)	45 (57.7%)
2	50 (34.7%)	18 (23.1%)
3	19 (13.2%)	9 (11.5%)
Baseline weight (kg)		
Mean (SD)	65.5 (14.33)	66.8 (13.32)
Median (min-max)	65.0 (36 – 114)	66.0 (40 – 94)
Height (cm)		
Mean (SD)	167.0 (10.04)	167.6 (8.64)
Median (min-max)	167.0 (141 – 204)	170.0 (135 – 187)
Time from progression to randomization (months)		
<3	131 (91.0%)	72 (92.3%)
3-6	8 (5.6%)	3 (3.8%)
>6	4 (2.8%)	1 (1.3%)
Missing	1 (0.7%)	2 (2.6%)
EGFR Activating Mutation result		
EGFR mutation	4 (2.8%)	7 (9.0%)
EGFR wild-type	36 (25.0%)	18 (23.1%)
Unknown	104 (72.2%)	53 (67.9%)
Weight loss in previous 6 months		
< 5%	93 (64.6%)	49 (62.8%)
5 – 10%	29 (20.1%)	16 (20.5%)
>10%	18 (12.5%)	9 (11.5%)
Unknown	4 (2.8%)	4 (5.1%)

Source: demog_squa.pdf

EGFR mutations are known to be more frequent among patients with female gender, who have never smoked, and with non-squamous histology subtype (Paz-Ares et al. 2010). To further evaluate the efficacy of erlotinib in a clinically selected population of patients highly likely to be EGFR wild-type, the MAH has conducted retrospective exploratory analyses of PFS and OS in the subgroup of male, smoker (or ex-smoker) patients with squamous NSCLC from the BR.21 study. In this subgroup, the incidence of EGFR-activating mutations would be expected to be even less frequent than in the overall squamous

NSCLC population. An overview of the demographic characteristics of patients in this subgroup is shown in Table 2. Forty-four percent of patients in the erlotinib group and 47.4% of patients in the placebo group were aged ≥65 years and most patients in both groups had an ECOG PS at randomization of 1 or 2. Of note, more patients than expected in both groups whose tissue samples were retrospectively tested for EGFR-activating mutations showed a positive test result (3/29 [10.3%] erlotinib patients; 5/21 [23.8%] placebo patients).

Table 2 Demographic data for the male, smoker subgroup of NSCLC patients with squamous cell histology in the BR.21 study

Parameter	Erlotinib N = 100	Placebo N = 57
Gender		
Male	100 (100%)	57 (100%)
Race		
White	84 (84.0%)	47 (82.5%)
Black	3 (3.0%)	4 (7.0%)
Oriental	9 (9.0%)	5 (8.8%)
Other	4 (4.0%)	1 (1.8%)
Age (years)		
18-39	1 (1.0%)	0
40-64	55 (55.0%)	30 (52.6%)
≥ 65	44 (44.0%)	27 (47.4%)
ECOG PS		
0	12 (12.0%)	2 (3.5%)
1	39 (39.0%)	35 (61.4%)
2	38 (38.0%)	12 (21.1%)
3	11 (11.0%)	8 (14.0%)
Baseline weight (kg)		
Mean (SD)	67.8 (14.15)	67.4 (12.58)
Median (min-max)	67.0 (43 – 114)	65.0 (40 – 94)
Height (cm)		
Mean (SD)	169.4 (8.45)	169.0 (6.81)
Median (min-max)	169.8 (150 – 204)	170.0 (152 – 185)
Time from progression to randomization (months)		
<3	91 (91.0%)	52 (91.2%)
3-6	6 (6.0%)	2 (3.5%)
>6	2 (2.0%)	1 (1.8%)
Missing	1 (1.0%)	2 (3.5%)
EGFR Activating Mutation result		
EGFR mutation	3 (3.0%)	5 (8.8%)
EGFR wild-type	26 (26.0%)	16 (28.1%)
Unknown	71 (71.0%)	36 (63.2%)
Weight loss in previous 6 months		
< 5%	62 (62.0%)	36 (63.2%)
5 – 10%	20 (20.0%)	12 (21.1%)
>10%	16 (16.0%)	6 (10.5%)
Unknown	2 (2.0%)	3 (5.3%)

Source: demog_male_squa_smoker.pdf

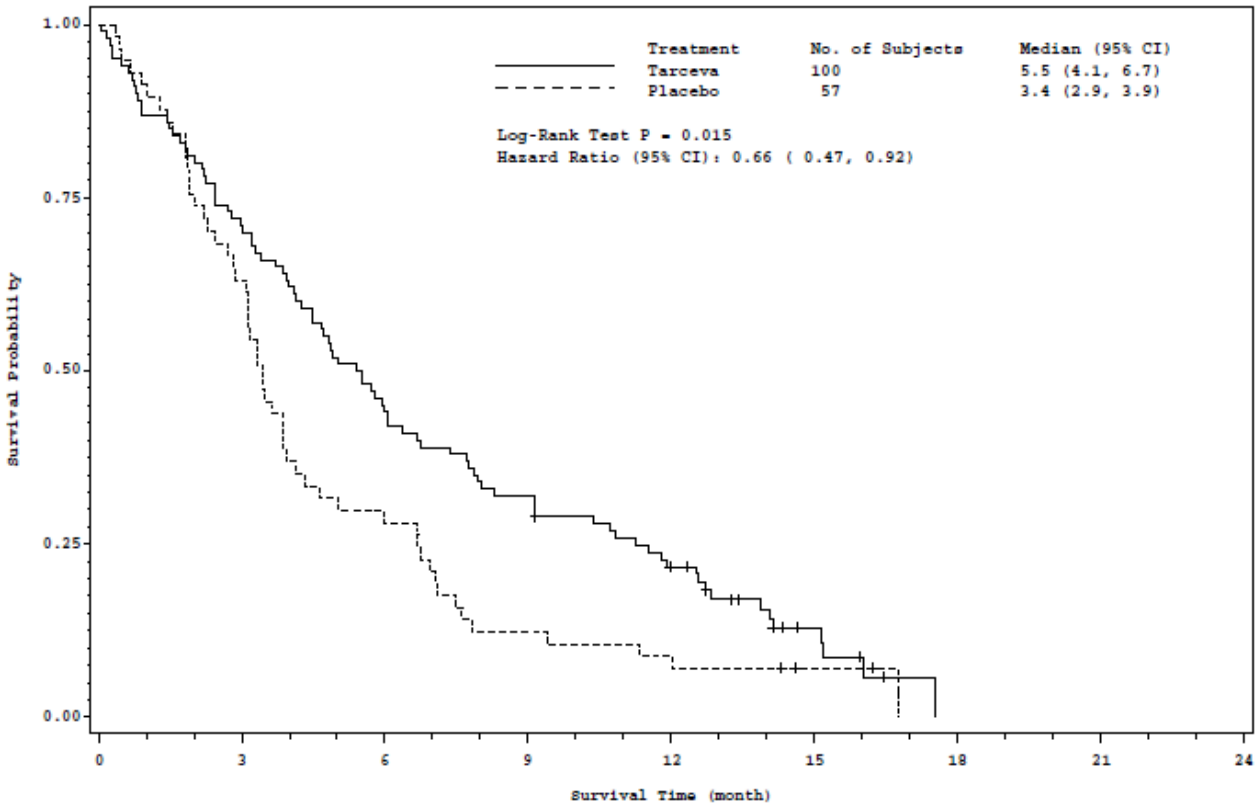
Results of the analyses of efficacy in this subgroup showed that median overall survival was 5.5 months (95% CI: 4.1, 6.7) in patients treated with erlotinib and 3.4 months (95% CI: 2.9, 3.9) in patients treated with placebo. The HR in favor of erlotinib was 0.66 (95% CI: 0.47, 0.92; exploratory p-value = 0.015) (Figure 2, upper panel).

With regards to progression free survival, median PFS was 2.4 months (95% CI: 2.0, 3.6) in patients treated with erlotinib and 1.8 months (95% CI: 1.6, 1.8) in patients treated with placebo with a HR in favor of erlotinib of 0.43 (95% CI: 0.30, 0.62; exploratory p-value < 0.001) (Figure 2, lower panel).

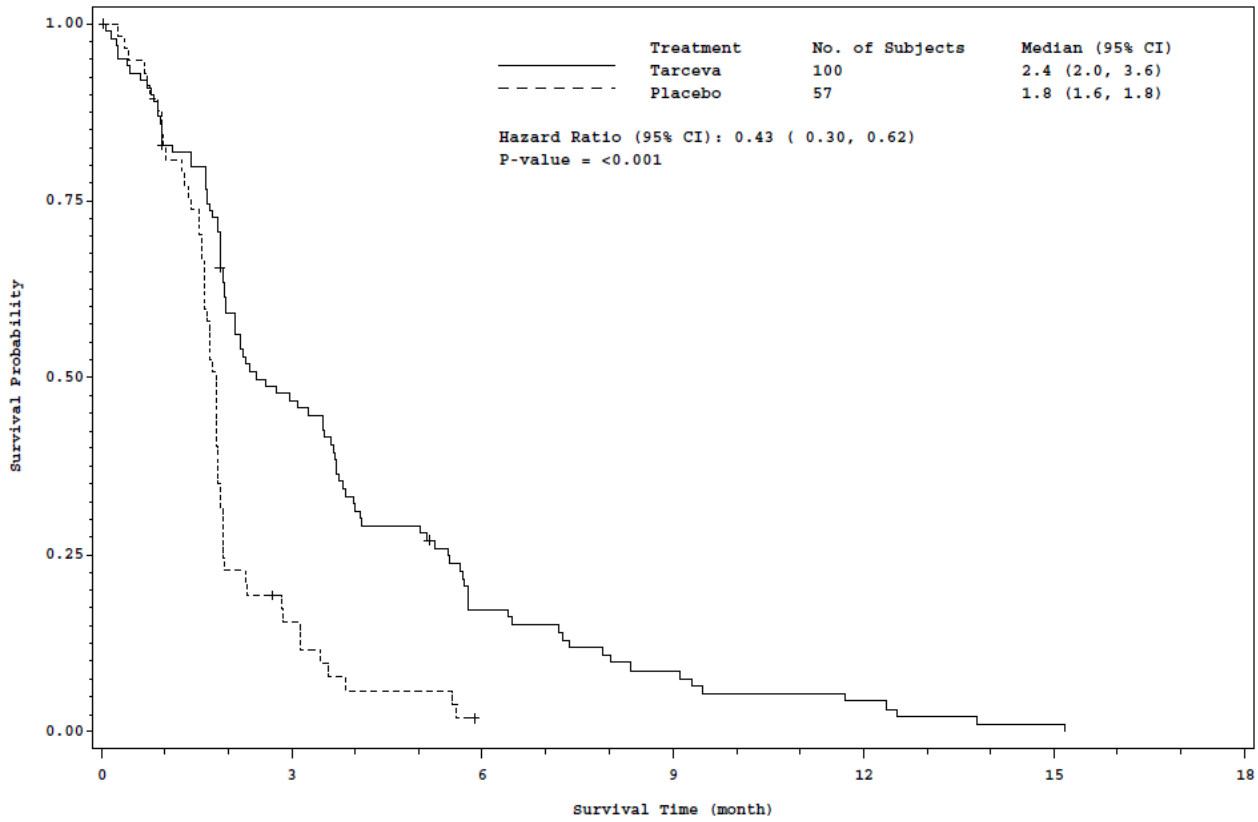
As concluded in multiple publications and NCCN guidelines, male smoker patients with squamous NSCLC subtype have a very low prevalence of EGFR mutations. Therefore this clinical selected subgroup can be viewed as a surrogate for an EGFR wild-type subgroup. These results are supporting evidence that erlotinib is effective in lowering the risk of death or risk of progression among EGFR wild-type patients when compared with best supportive care.

Figure 2 Kaplan-Meier curves of OS (upper panel) and PFS (lower panel) for the male, smoker subgroup of NSCLC patients with squamous cell histology in the BR.21 study

Overall Survival



Progression-Free Survival



CHMP comment

It was mentioned that a higher mutational rate was found in the BR.21 patients with squamous NSCLC as expected (16% vs 2.7%). Also the PEPiTA and the LUX-lung 8 study show higher mutation rates, 8% and 6%, respectively. The applicant is requested to provide an explanation of why this confirmed mutational testing was so much higher than expected for the BR.21 study and on how this high mutation rate affects the credibility of this subgroup analysis in respect to the efficacy of erlotinib in WT EGFR tumours.

In squamous cell lung cancers, high EGFR gene copy-number and protein overexpression are observed more frequently than in adenocarcinoma (82% versus 44%). Therefore, the increased efficacy in the squamous subgroup might be related to an increased EGFR expression level. The MAH is asked to provide EGFR expression data of the samples in this subgroup as well as efficacy results (PFS and OS) for patients with low and high expression level in the squamous NSCLC subgroups.

The MAH states that pre-clinical data suggest that the role of erlotinib might differ between maintenance and second-line treatment and this might be due to differential EGFR expression in chemotherapy-sensitive and a chemotherapy-resistant cells. The MAH is asked to perform subgroup analyses in the BR.21 study that could support this hypothesis. For instance, an efficacy (PFS and OS) analysis in patients that achieved a response or disease stabilization during the previous chemotherapy vs. patients progressing during previous chemotherapy.

The PEPiTA study

The **PEPiTA** (Patient EPIdermoïde Tarceva) study was a French multicenter, prospective, observational cohort, single-arm study in patients ≥ 18 years old with stage IIIB/IV squamous NSCLC who had failed first-line platinum based chemotherapy and had been prescribed erlotinib (150 mg/day) as second-line monotherapy [Monnet et al. 2016]. Patients were followed up for 12 months with clinic visits every 3 months and the primary objective was to determine PFS (based on RECIST 1.1 criteria) during the 12 month follow-up period. Secondary objectives included OS during the 12-month period, and to describe characteristics of erlotinib-treated patients, erlotinib treatment modalities, quality of life (QoL) evolution (FACT-L questionnaire) and erlotinib safety profile.

Characteristics of patients, erlotinib treatment modalities, progression of locally-advanced or metastatic disease, QoL data and safety data were analyzed using descriptive statistics. PFS and OS were analyzed using Kaplan-Meier methodology and prognostic factors for PFS analyzed with univariate and multivariate analysis using a Cox model.

A total of 152 patients were enrolled with 146 patients included in the efficacy population. Patients were mostly male (90%) with a mean age (± standard deviation) of 67.7 ± 8.6 years. The majority of patients were ex-smokers (64%) with 29% being smokers and 8% non-smokers. All patients had squamous (97%) or predominantly squamous (3%) NSCLC with disease stage IIIB (21%) or stage IV (79%). At enrolment, patients generally exhibited a poor ECOG PS (37% were Grade ≥ 2). Of 41/144 patients screened for EGFR mutations, 3 patients (7%) were positive. Overall, mean (± standard deviation) erlotinib treatment duration was 3.7 ± 3 months and treatment compliance was 99%.

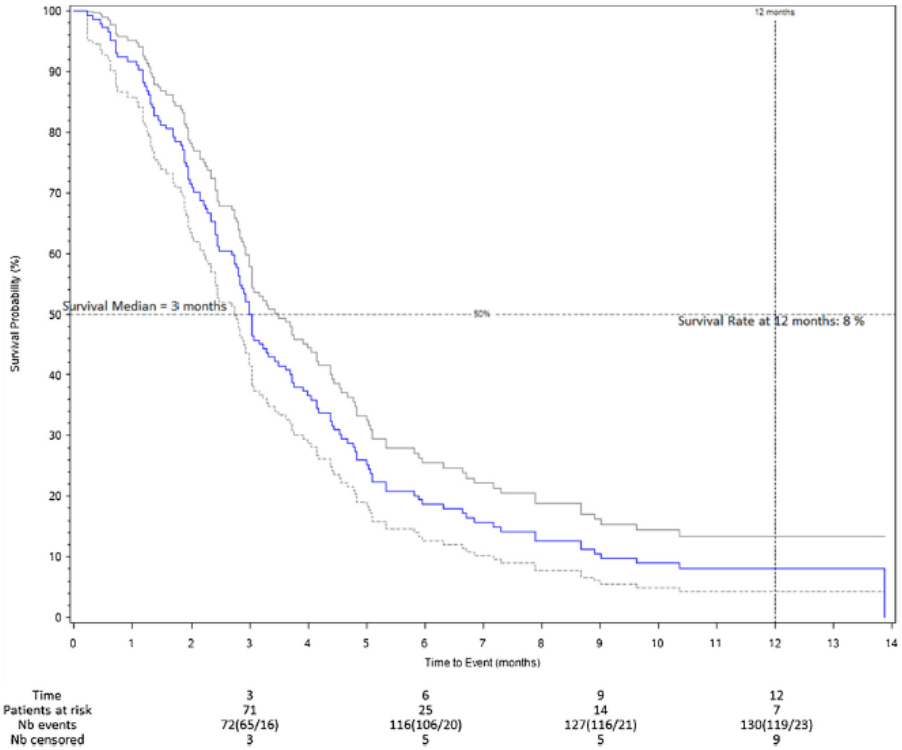
Median PFS was 3 months (95% CI: 2.7, 3.5 months) and median OS was 5.8 months (95% CI: 4.7, 7.1 months) (see

Figure 3).

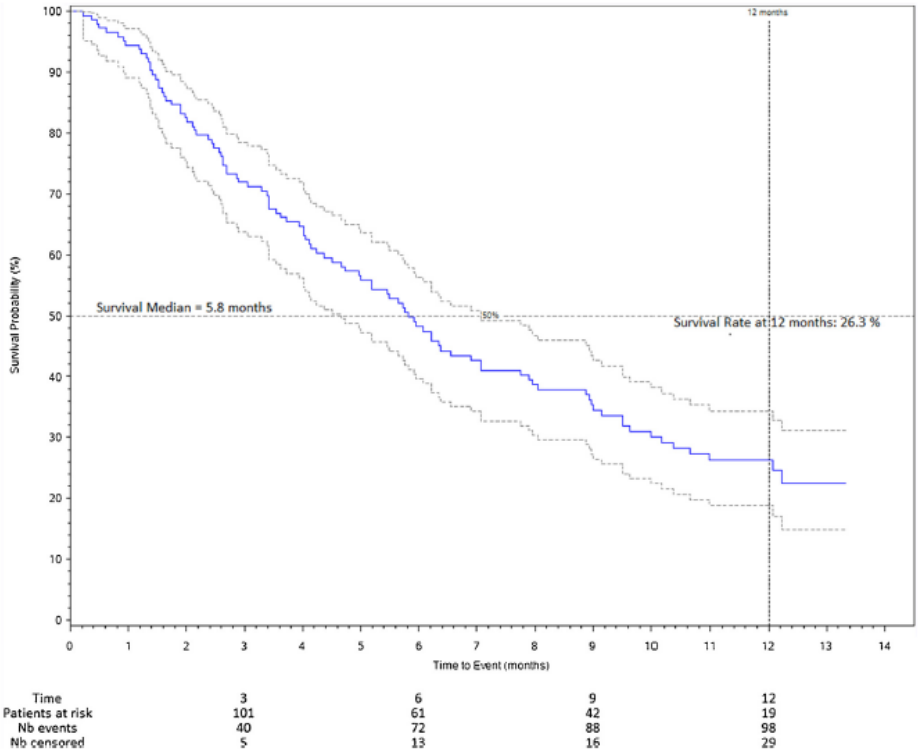
The results of this study with respect to PFS and OS are similar to those for BR.21, showing a consistent treatment benefit for erlotinib among male smoker NSCLC patients with squamous cell histology, a clinically selected population of EGFR wild-type patients.

Figure 3 Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in NSCLC patients with squamous histology in the PEPiTA study

PFS



OS



Source: Monnet et al. 2016

CHMP comment

The PEPiTA study is a propective observational single-arm study in patients with squamous NSCLC who had failed first-line therapy. These patients were subsequently treated with erlotinib. Only 8% were non-smokers. The MAH argues that observed median OS and PFS are in line with the findings in BR.21. Median OS was 5.8 months and median PFS was 3 months in the PEPiTA study. This is not endorsed. Median OS was 8.1 months in the EGFRwt subpopulation in BR.21.

The PEPiTa study is an observational study, and thus not controlled. Therefore, it is difficult to draw any solid conclusions.

The LUX-Lung 8 study

LUX-Lung 8 was an open-label, Phase 3, randomized, controlled study conducted at 183 cancer centers in 23 countries. The study was designed to compare the efficacy and safety of afatinib, a recently approved irreversible ErbB family inhibitor, with that of erlotinib in adult patients with Stage IIIB/IV squamous cell carcinoma who had progressed after at least 4 cycles of standard platinum-based first-line chemotherapy and were eligible for second-line therapy [Soria et al. 2015].

Patients were randomly assigned (1:1) to receive either afatinib (40 mg/day increased to 50 mg/day after 28 days for patients without any drug-related AEs) or erlotinib (150 mg/day) with randomization stratified by ethnic origin (eastern Asian versus non-eastern Asian) to eliminate potential bias in EGFR mutation bias across treatment groups. Tumor assessments were performed by computerized tomography (CT) or magnetic resonance imaging (MRI) at baseline and then at weeks 8, 12, 16 and every 8 weeks thereafter until confirmed progression or withdrawal for another reason. The primary endpoint was PFS (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) and the key secondary endpoint was OS. Other secondary endpoints included objective response rate, disease control rate, tumor shrinkage and patient-reported outcomes (EORTC QLQ-C30 and QLQ-LC13 questionnaires), although this latter endpoint was not reported.

The log-rank test (stratified by ethnic origin) was used to compare survival in the afatinib and erlotinib groups with a two-sided α of 0.05. A Cox proportional hazard model was used to estimate the HRs and corresponding 95% CIs for survival; Kaplan-Meier estimates and 95% CIs were calculated with Greenwood's standard error estimate. Logistic regression models, also stratified by ethnic origin, were used to compare overall response rate and disease control rate between groups.

A total of 795 patients were enrolled; 398 patients randomized to afatinib and 397 patients randomized to erlotinib. Baseline characteristics were generally well balanced between the treatment groups. Median age was 64 years in the erlotinib group and 65 years in the afatinib group. More than 80% of patients in each group were male and the majority of patients in each group were ex-smokers (71% and 71%, respectively) with 21% and 18%, respectively being current smokers.

The primary analysis of PFS was performed with a median follow-up of 6.7 months (interquartile range [IQR] 3.1-10.2 months) at which time statistical significance was only just met showing a PFS benefit for afatinib over erlotinib (HR = 0.82 [95% CI: 0.68, 1.00]; p = 0.0427). Median PFS was 2.4 months (95% CI: 1.9, 2.9) in the afatinib group versus 1.9 months (95% CI: 1.9, 2.2) in the erlotinib group (Figure 4, upper panel).

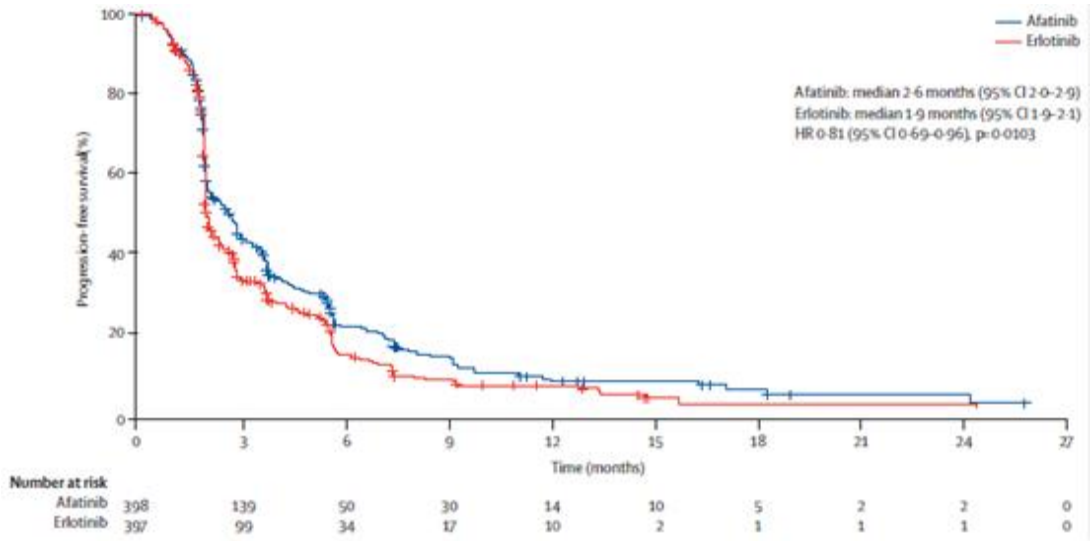
At the time of the primary analysis for OS (median follow-up of 18.4 months (IQR 13.8-22.4 months), afatinib showed a modest improvement in survival versus erlotinib (HR = 0.81 [95% CI: 0.69, 0.95]; p

= 0.0077) with a median OS of 7.9 months (95% CI: 7.2, 8.7 months) in the afatinib group and a median OS of 6.8 months (95% CI: 5.9, 7.8 months) in the erlotinib group (Figure 4, lower panel).

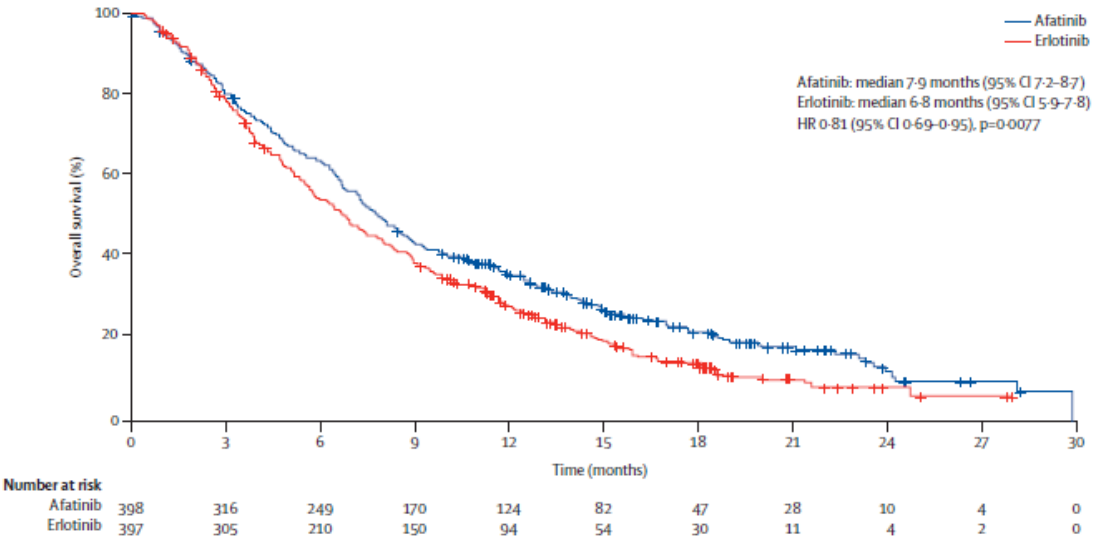
The results of this study demonstrate that while afatinib appears to show a modest improvement over erlotinib with respect to PFS and OS in patients with squamous NSCLC, a treatment effect in the erlotinib control arm is still observed which is consistent with that seen for the BR.21 subgroup analysis of male, smoker patients with squamous histology.

Figure 4 Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in patients with squamous NSCLC in the LUX-Lung 8 study

PFS



OS



Source: Soria et al. 2015

CHMP comment

The lack of a control containing placebo in the above LUX-lung 8 study does not allow to draw any conclusion regarding the claimed activity of erlotinib in the patients enrolled in the study. The proposed inter-study comparison with BR.21 is not considered methodologically appropriate and therefore not acceptable. A very limited median PFS reported with erlotinib (1.9 months) is observed, indicating that the great majority of patients experienced disease progression at the time of the first radiological evaluation during the study.

Single Arm Study of Erlotinib in Second- and Further-Line Treatment of NSCLC - The TRUST study

The **TRUST study** was a large, international, Phase 4, open-label, single-arm study of erlotinib treatment in an unselected patient population (N = 6580) with histologically or cytologically confirmed, unresectable, Stage IIIB/IV NSCLC who had received at least one course of standard chemotherapy or radiotherapy or were unsuitable for chemotherapy [Reck et al. 2010]. Erlotinib (150 mg) was administered once daily to all patients until disease progression, unacceptable toxicity, or death. The primary objective of the study was to provide access to erlotinib (before approval) for patients with stage IIIB/IV NSCLC who had failed or were unsuitable for chemotherapy or radiotherapy. Secondary objectives were to assess safety, best response, PFS, and OS. The incidence and severity of erlotinib-related rash was also a secondary endpoint for the study which was conducted in a large patient population, with broad inclusion and exclusion criteria, across a number of countries with differences in clinical practice.

An analysis of efficacy outcomes (PFS, OS and Best Response per investigator assessment) was performed in a subpopulation of 3224 patients from this study who received erlotinib as second-line therapy [Heigener et al. 2011]. The majority of patients in this subpopulation had stage IV NSCLC (78%) and an ECOG PS of 0 or 1 (78%). Median age was 62 years (range 19-90 years) and most patients (60%) were male. Former or current smokers comprised 68% of the population with 32% of the patients being non-smokers. The most common NSCLC histologies were adenocarcinoma (56%) or squamous-cell carcinoma (22%).

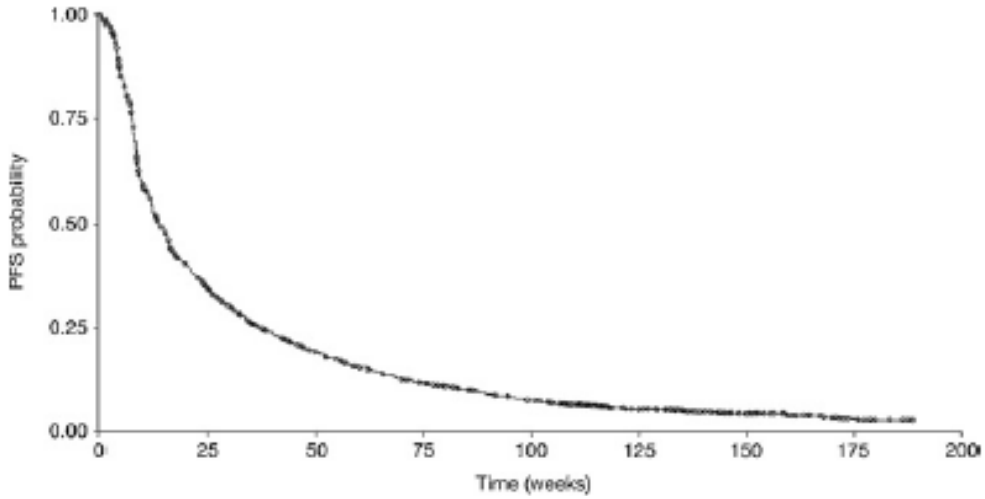
Response data were available for all 3224 patients. A complete response (CR) was achieved in 25 patients (<1%), while partial response (PR) was achieved in 368 patients (14%) and stable disease (SD) in 1444 patients (54%) for an overall disease control rate of 68%.

Median PFS was 13.6 weeks (95% CI: 12.9, 14.9 weeks) (Figure 5, upper panel) and median OS was 8.6 months (95% CI: 8.2, 9.2 months) (Figure 5, lower panel). EGFR mutation analyses were performed for patients providing tumour specimens (from initial diagnosis) using PCR-based bi-directional sequencing [Heigener et al. 2010]. Within the second-line patient population, 138 patients had known EGFR mutation status and only 18 of those (13%) had EGFR mutation-positive disease, suggesting that the results of the study were not just EGFR-activating mutation dependent. This was further supported by the fact that most patients treated in the second-line developed erlotinib-related rash (~77%) and the progression-free survival and overall survival in patients experiencing rash was longer compared to those with no rash with HR=0.52 (95% CI: 0.48 - 0.57) and 0.50 (95% CI: 0.45 - 0.55), respectively.

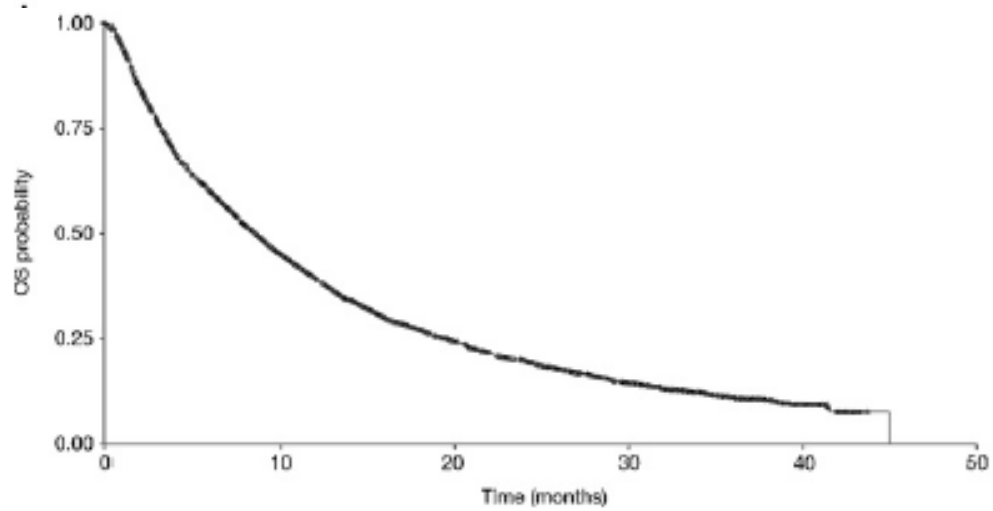
The study confirmed the efficacy of erlotinib in a broad patient population (those with and without EGFR-activating mutations and those whose EGFR mutation status was unknown).

Figure 5 Kaplan-Meier Curves of PFS (upper panel) and OS (lower panel) in NSCLC patients from the TRUST study (Overall Population)

PFS



OS



Source: Heigener et al. 2011

CHMP comment

The TRUST study was a large phase 4, single-arm study in unselected patients, who have failed first-line therapy or who were unsuitable for chemotherapy. Of these, 3224 patients received erlotinib as second-line therapy. Only 138 patients had known EGFR mutation status and only 18 of those has EGFRmut. The median OS was 8.6 months. Thus, the MAH concludes that the study confirms the efficacy of erlotinib in a broad patient population.

There are several uncertainties/limitations of this study. First of all, the mutation status is unknown in the majority of patients. Secondly, the majority of the patients had adenocarcinoma, were EGFRmut are more likely. Thirdly, the study is not controlled and included unselected patients. Thus, the conclusions of the MAH are not endorsed. It is not possible to conclude that this study supports the findings in study BR.21.

Studies of Erlotinib versus Chemotherapy in Second- and Further-Line Treatment of NSCLC Patients with EGFR wild-type Tumors

Although many randomized controlled trials comparing erlotinib and chemotherapy in second- and further-line treatment have been conducted, only two trials have prospectively investigated the effect of Tarceva versus chemotherapy in EGFR wild-type patients [Li et al. 2014, Garassino et al. 2013].

Phase II study of Erlotinib versus Pemetrexed in Second-Line Treatment of NSCLC

Li et al. [2014] conducted a prospective, randomized, open-label, Phase 2 study comparing erlotinib with pemetrexed as second-line therapy in patients with advanced EGFR wild-type and EGFR fluorescence in-situ hybridization (FISH)-positive lung adenocarcinoma. EGFR mutations were assessed by the amplification-refractory mutation system (ARMS) method and patients were classified as EGFR mutation-negative if they did not have an EGFR mutation. FISH positivity was defined as high polysomy or gene amplification.

Patients (18-75 years) with an ECOG PS 0-2 with EGFR wild-type and EGFR FISH-positive disease who had received 1 prior platinum-based chemotherapy regimen were randomized in a 1:1 ratio to receive erlotinib (150 mg/day) or pemetrexed (500 mg/m^2 on day 1 of a 3-weekly treatment cycle) until disease progression, unacceptable toxicity or discontinuation by the patient. Randomization was stratified by sex (female vs male), EGOG PS (0 to 1 vs 2) and smoking history (never vs ever) using a minimization method. The primary endpoint of the study was PFS with secondary endpoints including OS, overall response rate (ORR), and safety and tolerability.

The Kaplan-Meier method was used to estimate PFS and OS. The log-rank test was used to compare PFS and OS between the 2 treatment groups. Preplanned subgroup analysis with the Cox proportional hazards model, including sex, smoking history, ECOG performance status, and best response to the prior chemotherapy, was used to estimate the HR for PFS and OS. The chi-square test or Fisher exact test was used to compare the ORRs and adverse events (AEs) between the two treatment groups.

Of the 497 patients screened, 302 were identified with EGFR wild-type disease. Of these, 123 patients who were both EGFR wild-type and EGFR-FISH positive were randomized to treatment with erlotinib (n = 61) or pemetrexed (n = 62). The treatment groups were well matched for baseline characteristics including sex, ECOG PS, disease stage and smoking history. Median age was 54 years in the erlotinib group and 55 years in the pemetrexed group. The majority of patients in each group were male (66% and 63%, respectively) and most patients in each group were current smokers (64% and 65%, respectively) with 25% and 27%, respectively being non-smokers.

Median PFS was 4.1 months (95% CI: 1.6, 6.6) in the erlotinib group and 3.9 months (95% CI: 2.7, 5.1) in the pemetrexed group and 6-months PFS rates were 45.1% and 38.8%, respectively (Figure 6, upper panel). The difference in PFS between the treatment groups was not statistically significant (HR = 0.92 [95% CI: 0.62, 1.37]; p = 0.683).

The median OS was 11.7 months (95% CI: 7.5, 15.9) in patients treated with erlotinib and 13.4 months (95% CI: 9.2, 17.7) in patients treated with pemetrexed (Figure 6, lower panel). The difference in OS was not significant between the pemetrexed and Tarceva treatment groups (HR = 1.01 [95% CI: 0.66, 1.54]; p-value = 0.97).

PFS and OS results were consistent across all pre-planned subgroups.

Per the investigator's assessment, 12/61 (19.7%) patients in the erlotinib group and 5/62 (8.1%) patients in the pemetrexed arm experienced an objective response. All objective responses were PRs

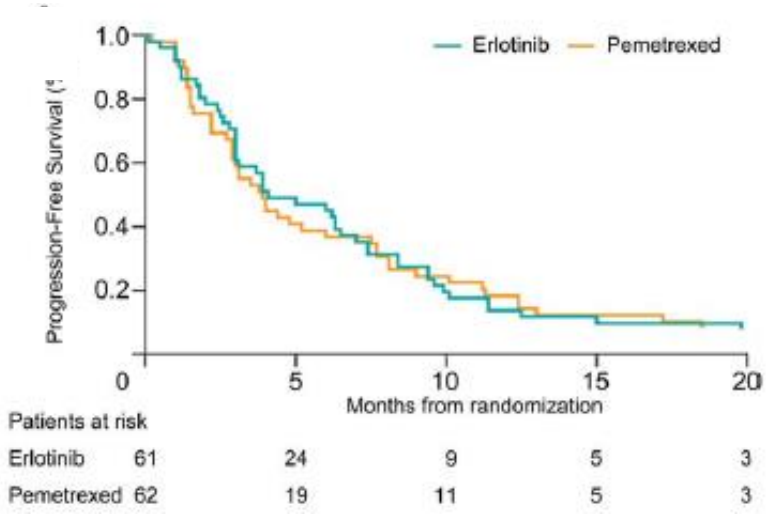
and no CR was reported. In general, the ORR was higher among patients treated with erlotinib although the difference between treatment groups was not statistically significant (p-value = 0.062).

Post-study treatment was based on a decision of the physicians and patients. Of the patients who failed second-line pemetrexed, 61% crossed over to erlotinib and 15% crossed over to docetaxel. Of the patients who failed second-line erlotinib, 48% crossed over to chemotherapy (23% pemetrexed; 25% docetaxel).

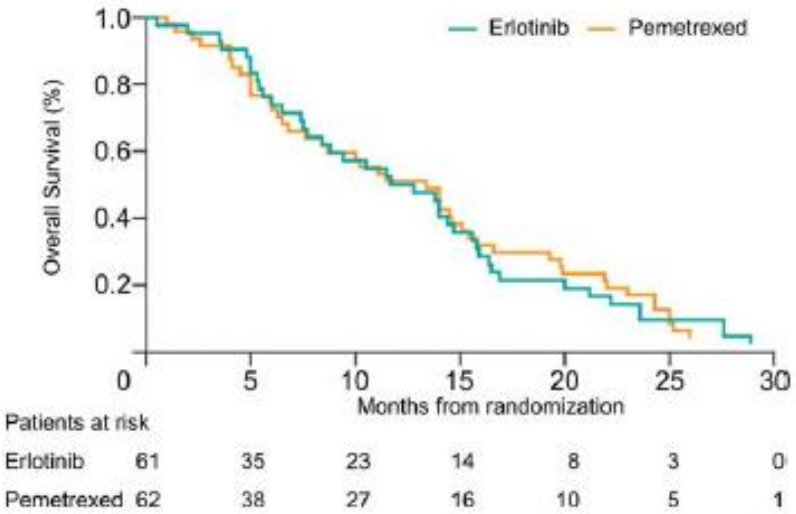
The authors concluded that in this study there were no significant differences with regards to efficacy between erlotinib and pemetrexed in the second-line setting for patients with advanced EGFR wild-type and EGFR FISH-positive lung adenocarcinoma and that both regimens appear to be effective treatment options for patients.

Figure 6: Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in NSCLC Patients with EGFR wild-type and EGFR-FISH-positive tumors receiving second-line treatment with erlotinib or pemetrexed

PFS



OS



Source: Li et al. 2014

CHMP comment:
The results of this study, showing no statistical significant difference between erlotinib and pemetrexed in a NSCLC population without EGFR mutation and with positive FISH, could support the hypothesis suggested by the MAH that high EGFR expression could be associated with erlotinib anti-tumour activity. A selection bias (i.e., exclusion of patients with EGFR FISH negative tumours) could explain the relatively long median OS observed in this study.

TAILOR study

The **Tarceva Italian Lung Optimization Trial (TAILOR) trial** was a prospective, multicenter, randomized study comparing second-line treatment with erlotinib versus second-line treatment with docetaxel in advanced NSCLC patients with EGFR wild-type tumors who had failed first-line platinum-based chemotherapy [Garassino et al. 2013]. The study was conducted at 52 Italian centers. EGFR mutational status of exons 19-21 was determined using both Sanger sequencing and RFLP at two independent laboratories and the Scorpion/ARMS technique was used for samples with limited material. Patients with EGFR mutations were excluded from the study.

Eligible patients were randomly assigned on a 1:1 basis to treatment with erlotinib (150 mg/day) or docetaxel (75 mg/m^2 every 21 days or 35 mg/m^2 on days 1, 8 and 15 every 28 days). Randomization was stratified by center, disease stage, type of first-line platinum-based chemotherapy (pemetrexed vs vinorelbine vs gemcitabine), and ECOG PS (0-1 vs 2). The study did not permit treatment crossover after further disease progression.

The trial was initially designed to assess the different effects of docetaxel and erlotinib according to selected biomarkers (EGFR amplification and protein expression, and KRAS mutations). At the first planned interim analysis, the independent monitoring committee recommended changing the primary objective to a comparison of efficacy between the two treatment groups as the pre-planned interim efficacy analysis, in conjunction with other data, had suggested that the proposed biomarkers had no effect. Consequently, the protocol was amended, the primary objective changed and the sample size was recalculated by two independent statisticians. The revised primary endpoint following the protocol amendment was OS and secondary endpoints included PFS, response rate and QoL. Time to event data were analyzed by the Kaplan-Meier method and the Cox proportional hazards model was used to adjust the treatment effect for histology, smoking habit, ECOG PS, sex, best response to first-line chemotherapy, and KRAS mutational status. Proportional hazards assumptions for Cox models were verified through graphical plots of Schoenfeld residuals over time, by adding time-dependent variables in the model and testing their statistical significance. A further analysis was done to assess possible treatment effects by factor interactions using the χ^2 test for heterogeneity and described with Forest plots.

Of the 702 patients screened, 540 were genotyped. Of these, 222 patients with EGFR wild-type were randomized to receive docetaxel (n = 110) or erlotinib (n = 112). The treatment groups were well matched for baseline characteristics including sex, ECOG PS, histology and smoking history. Median age was 66 years in the erlotinib group and 67 years in the docetaxel group. The majority of patients in each group were male (71% and 66%, respectively) and most patients in each group were current or former smokers (83% and 73%, respectively) with 17% and 27%, respectively being non-smokers.

After a median follow up of 33 months [IQR 21-33 months], 196 patients had experienced progressive disease (PD) and 187 patients had died. Median OS was 8.2 months (95% CI 5.8, 10.9) in the docetaxel group and 5.4 months (95% CI: 4.5, 6.8) in the erlotinib group (Figure 7, lower panel). The unadjusted OS HR of docetaxel to erlotinib was 0.78 (95% CI: 0.51, 1.05; p = 0.1) and the adjusted OS HR was 0.73 (95% CI: 0.53, 1.00; p = 0.05). Median PFS was 2.9 months (95% CI 2.4, 3.8) in the docetaxel group and 2.4 months (95% CI: 2.1, 2.6) in the erlotinib group (Figure 7, upper panel). The unadjusted PFS HR of docetaxel to erlotinib was 0.72 (95% CI: 0.55, 0.94; p = 0.01) and the adjusted PFS HR was 0.71 (95% CI: 0.53, 0.95; p = 0.02).

Outcomes across all subgroups were consistent with the overall analyses although many of the differences were not statistically significant.

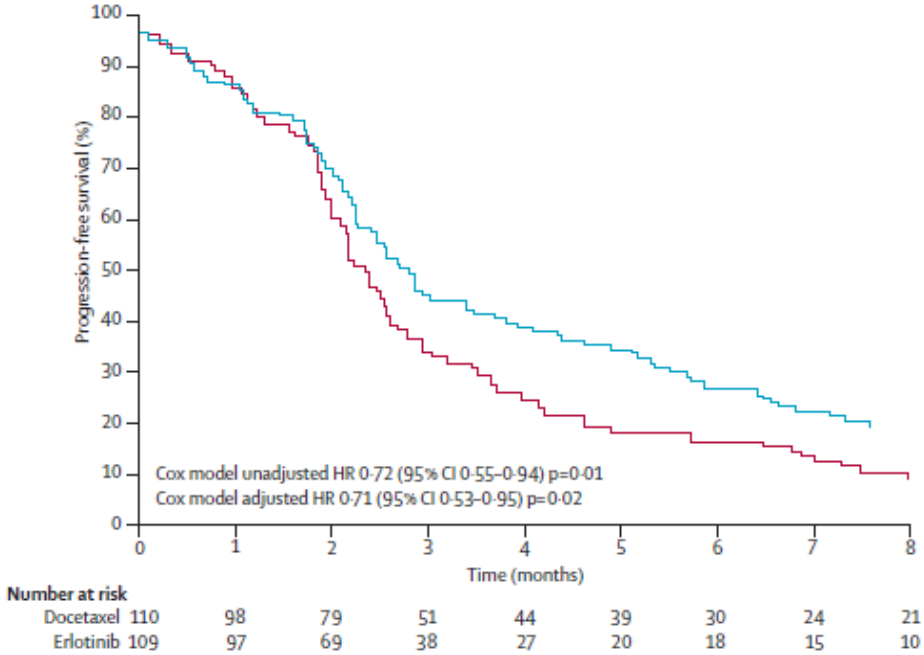
Fifteen patients (15.5% [95% CI: 8.9, 24.2]) in the docetaxel group had an objective response to treatment, compared with 3 patients (3.0% [95% CI: 0.6, 8.5%]) in the erlotinib group (p = 0.003) while 43 patients (44.3% [95% CI: 31.4, 52.1]) in the docetaxel group achieved disease control versus 26 patients (26.0% [95% CI: 17.7, 35.7]) in the erlotinib group (p = 0.007). Investigator assessments of response were confirmed by post-hoc independent review in 94.4% of cases (three in the erlotinib group and 14 in the docetaxel group).

Of note, tumor samples from the three patients in the erlotinib group who had responses were re-sequenced from the original biopsies in a post-hoc assessment, confirming the absence of mutations in EGFR exons 18-21.

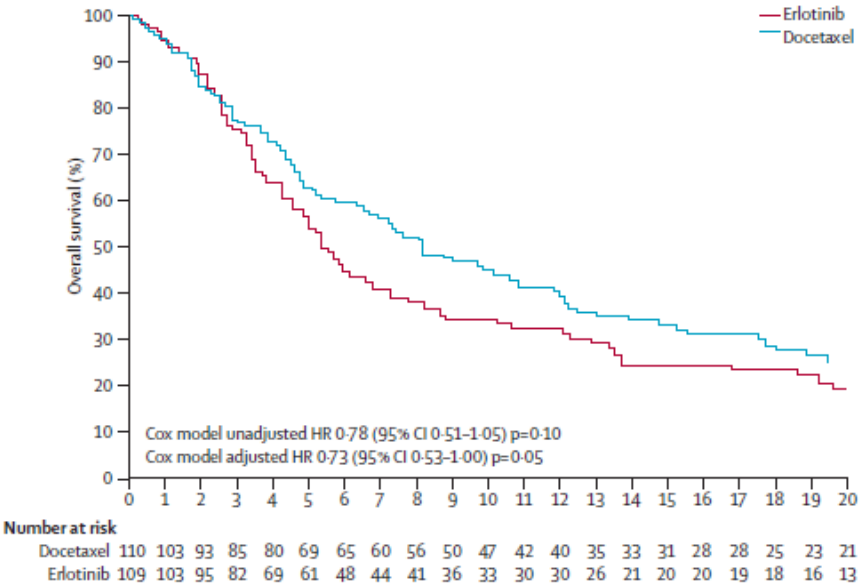
In contrast to the results of the study by Li et al. as well as other studies in which the efficacy of erlotinib versus chemotherapy has been evaluated in the subpopulation of EGFR wild-type patients selected from the overall enrolled study population, results of the TAILOR study suggested that chemotherapy is more effective than erlotinib for second-line treatment in previously treated patients with NSCLC who have EGFR wild-type tumors. At the time of publication, however, there were substantial concerns raised regarding the study design and conduct of the trial, suggesting that the outcome of this study should be interpreted with caution (Moro-Sibilot et al. 2014; Dafni et al. 2014)

Figure 7 Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in NSCLC patients with EGFR wild-type in the TAILOR study

PFS



OS



Source: Garassino et al. 2013

CHMP comment

The TAILOR study was a randomised study investigating erlotinib vs. docetaxel in second-line setting in patients with NSCLC EGFRwt. EGFR mutation status was determined upfront, and patients with EGFRmut were excluded from the study. In total 222 patients with EGFRwt were randomised 1:1. Median OS was 8.2 months and 5.4 months in the docetaxel and erlotinib arms respectively. Thus, in contrast to BR.21 and the Li et al study, this study seems to suggest that chemotherapy is better than erlotinib in second-line in WT-EGFR patient. However, as emphasised by the MAH, there were several concerns raised in relation to the study design and the conduct of the study. The study design was

changed at the time of the blinded interim OS results were known, lack of adjustment for multiplicity, exclusion of patients with prior exposure to taxanes (included patients may not represent truly second-line patients).

TITAN study

TITAN (Tarceva in Treatment of Advanced NSCLC) was a multicenter, international, open-label Phase 3 study of erlotinib versus chemotherapy (single-drug docetaxel or pemetrexed) as second-line treatment for advanced NSCLC patients whose disease progressed during or immediately after first-line treatment with platinum-doublet chemotherapy.

The study was performed at 77 centers in 24 countries. Patients were randomly assigned 1:1 to receive erlotinib (150 mg/day) or second-line chemotherapy (standard docetaxel or pemetrexed dosing schedule, at the discretion of the treating physician). Randomization was stratified by stage of disease at start of treatment (IIIb versus IV), ECOG PS (0 or 1 versus 2), smoking history (present versus past versus never) and region (North America, South America, Western Europe, Eastern Europe, Southeast Asia, and Africa). Treatment was continued until unacceptable toxicity, disease progression or death.

The study was halted prematurely due to slow recruitment and results reported after a median follow up of 27.9 months in the erlotinib arm and 24.8 months in the chemotherapy arm [Ciuleanu et al. 2012]. The statistical plan was modified after premature cessation of the trial and the power of the statistical analyses to detect a difference in OS between treatments was reduced to 60%, therefore some of the analyses were underpowered to detect clinically meaningful treatment effects. The primary endpoint was OS and secondary endpoints included PFS and time to progression (TTP). QoL was assessed with the FACT-L, version 4 questionnaire. For analyses of the primary and secondary endpoints, median values and 95% CIs were estimated by Kaplan-Meier methodology; two-sided log-rank tests were used to compare treatment groups. Overall response (complete or partial) rates and associated 95% CIs were calculated by the Pearson-Clopper method. Overall response rates were compared by a χ^2 test. Additionally, 95% CIs for the difference were calculated with the Anderson-Hauck approach.

Of the 424 patients enrolled in the study, 203 were randomized to erlotinib and 221 were randomized to chemotherapy (116 to docetaxel; 105 to pemetrexed). The overall study population had a median age of 59 years (range 22-80 years) and baseline characteristics were generally well balanced between the treatment groups. However, the erlotinib group included a higher percentage of males (79% versus 72%), patients with squamous cell carcinoma (38% versus 35%), patients with stage IV disease (80% versus 77%), and present smokers (56% versus 51%) than the chemotherapy group, whereas the proportion of patients who had never smoked was lower in the erlotinib group than the chemotherapy group (15% versus 20%, respectively). Additionally, the chemotherapy group had a higher percentage of patients with ECOG PS 1-2 than the erlotinib group (90% versus 86%, respectively). Although tumor sampling was mandatory in the TITAN study, because of the limited amount of tumor tissue, molecular analyses were prioritized such that EGFR mutational status was determined in only 55% of patients (115/203 [57%] erlotinib patients and 120/221 [54%] chemotherapy patients). Mutational analysis was determined using DNA lysates from macro-dissected or micro-dissected tissue samples with a minimum tumor cell content of 60%. Exons 18-21 of the EGFR gene were amplified by PCR using nested primers, and multiple independent products were sequenced on both strands. Of note, only a small number of patients tested had confirmed EGFR

activating mutations (7/115 [6%] and 4/120 [3%] in the erlotinib and chemotherapy groups, respectively).

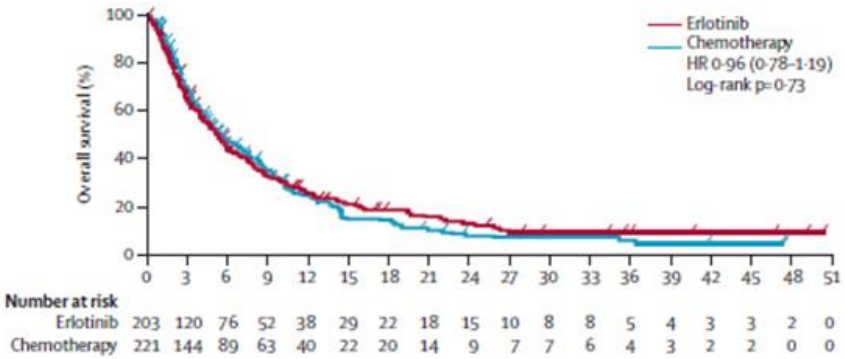
At the time of the primary analysis, in the overall population median OS was 5.3 months (95% CI: 4.0, 6.0) in the erlotinib group and 5.5 months (95% CI: 4.4, 7.1) in the chemotherapy group (HR = 0.96; 95% CI: 0.78, 1.19; p = 0.73) (Figure 8, upper panel). Median PFS was 6.3 weeks (95% CI: 6.1, 6.9) in the erlotinib group versus 8.6 weeks (95% CI: 7.1, 12.1) in the chemotherapy group (HR = 1.19; 95% CI: 0.97, 1.46; p = 0.089) (Figure 9, upper panel). Furthermore, no statistically significant difference in the time to symptom progression (HR = 1.19; 95% CI: 0.90, 1.57) or time to deterioration (HR = 1.21; 95% CI 0.93, 1.59) in quality of life (FACT-L) was observed between the two treatment groups. The proportion of patients with a partial response was similar between treatment groups: 7.9% (95% CI: 4.6, 12.5) in the erlotinib group and 6.3% (95% CI: 3.5, 10.4) in the chemotherapy group (p = 0.53). No complete responses were reported.

Further-line treatment following disease progression was at the discretion of the investigator and was balanced across the treatment groups. Of the patients who failed second-line chemotherapy (pemetrexed or docetaxel), 23% crossed over to tyrosine kinase inhibitors (TKIs) with 20% receiving erlotinib. Of the patients who failed second-line erlotinib, 25% crossed over to antimetabolites and 23% crossed over to taxanes.

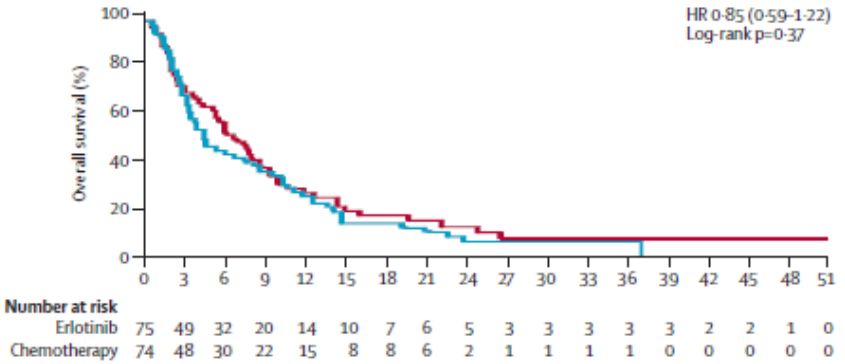
A subgroup analysis of 149 patients with confirmed EGFR wild-type tumors showed that, consistent with the overall population results, there was no significant difference in the primary efficacy endpoint of OS between the erlotinib and chemotherapy treatment arms with a HR = 0.85 (95% CI: 0.59, 1.22; p = 0.37)(Figure 8, lower panel). Similarly, there was no difference in PFS between the two treatment arms (HR = 1.25; 95% CI: 0.88, 1.78; p = 0.20) (Figure 9, lower panel). There were too few patients with EGFR-activating mutations to interpret any efficacy data and draw valid conclusions.

Figure 8: Kaplan-Meier curves of OS in NSCLC patients in the overall population (upper panel) and subpopulation of patients with EGFR wild-type (lower panel) in the TITAN study

Overall Population



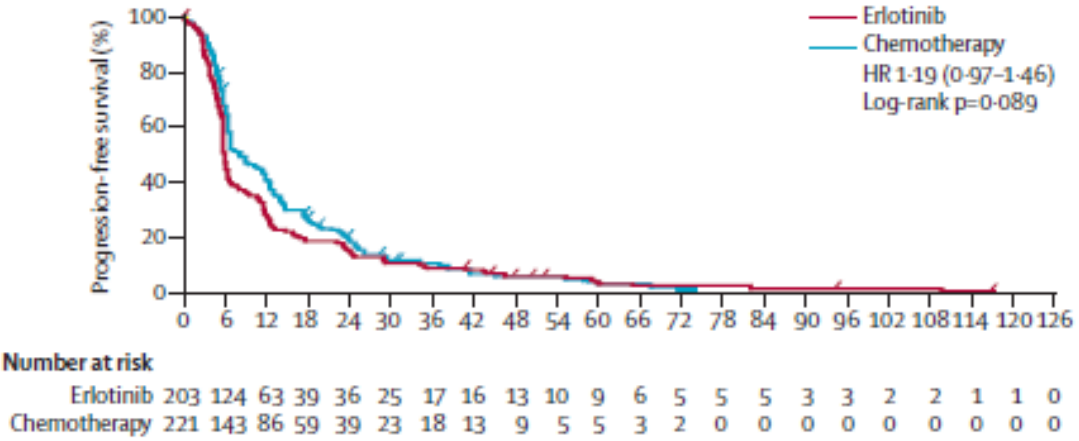
EGFR wild-type patients



Source: Ciuleanu et al. 2012

Figure 9: Kaplan-Meier curves of PFS in NSCLC Patients in the overall population (upper panel) and subpopulation of patients with EGFR wild-type (lower panel) in the TITAN study

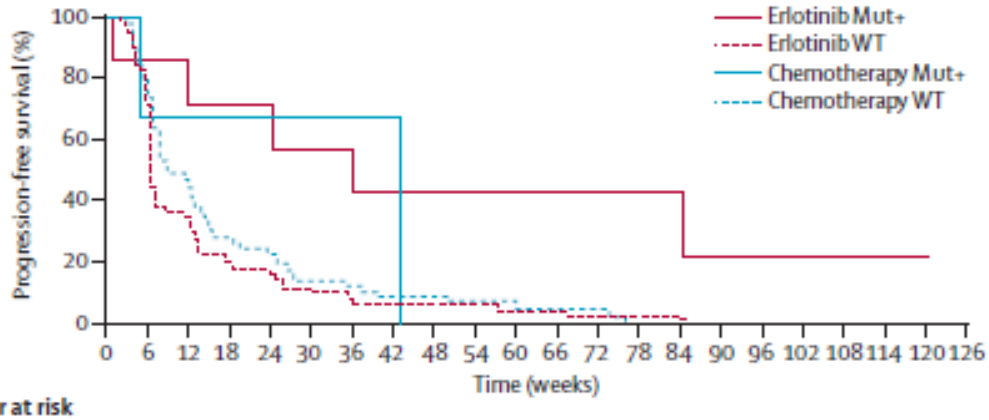
Overall Population



Number at risk

Erlotinib	203	124	63	39	36	25	17	16	13	10	9	6	5	5	5	3	3	2	2	1	1	0
Chemotherapy	221	143	86	59	39	23	18	13	9	5	5	3	2	0	0	0	0	0	0	0	0	0

EGFR wild-type patients



Number at risk

Erlotinib Mut+	7	6	5	5	5	4	4	3	2	2	2	2	2	2	2	1	1	1	1	1	1	0
Erlotinib WT	75	48	24	14	12	8	3	3	3	3	2	2	1	1	1	0	0	0	0	0	0	0
Chemotherapy Mut+	4	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chemotherapy WT	74	45	28	17	13	8	7	5	5	3	3	2	2	0	0	0	0	0	0	0	0	0

Source: Ciuleanu et al. 2012

CHMP comment:

The TITAN study shared a first-line chemotherapy run-in phase with the phase 3 SATURN study of maintenance therapy with erlotinib. Patients with controlled disease were offered entry into SATURN and those with disease progression while receiving first-line doublet chemotherapy—representing a population with poor prognosis—were offered entry into TITAN. Once SATURN had been fully recruited, overall recruitment slowed considerably. As a result, enrolment into TITAN was halted prematurely. The power of the statistical analyses to detect a difference in OS between treatments was reduced to 60%, therefore some of the analyses were underpowered to detect clinically meaningful treatment effects.

The TITAN study is a study in patients progressing on or immediately after first-line chemotherapy. That would suggest that this is a group of patients with "chemo-resistant" tumours (and therefore

possibly high EGFR expression as suggested by the applicant). In general, no significant difference was detected between the chemotherapy and erlotinib in the WT subgroup. However, no conclusion can be made as analyses were underpowered due to the limited sample size related to premature stop of the trial.

DELTA study

The **Docetaxel and Erlotinib Lung Cancer Trial (DELTA) study** was a multicenter, open-label, randomized, phase 3 study conducted in 41 centres across Japan evaluating the efficacy and safety of erlotinib versus docetaxel as second- or third line therapy in unselected patients with advanced NSCLC [Kawaguchi et al. 2014]. Patients ≥20 years of age with stage IIB/IV NSCLC whose disease had progressed following previous treatment with one or two chemotherapy regimens, including at least one platinum agent, were randomly assigned 1:1 to receive erlotinib (150 mg/day) or docetaxel (60 mg/m^2 every 3 weeks [Q3W]) until disease progression or intolerable toxicity. Randomization was stratified by sex, performance status, histology and institution. The primary endpoint of the study was PFS and secondary endpoints included OS, tumour response, safety, and analyses of EGFR wild-type and EGFR mutant tumours.

Time to event analysis was performed using the Kaplan-Meier method and a log-rank test was used to compare treatment groups. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowley. Estimates of the treatment effect were expressed as HRs and two-sided 95% CIs from a Cox regression model for erlotinib versus docetaxel. Mutational analysis was performed by a commercial laboratory using a highly sensitive PCR-based method (i.e., the PCR-invader method, peptide nucleic acid-locked nucleic acid PCR clamp method, or cycleave method). A prospective analysis of PFS and OS in patients with EGFR wild-type and EGFR mutant tumours was performed as a secondary endpoint. To assess the homogeneity of the treatment effect on PFS and OS, an interaction term of treatment and EGFR mutation status (wild-type, exon 19 deletion or L858R, or other) was evaluated in a Cox model using the likelihood ratio test.

A total of 301 patients were enrolled and randomized to treatment with erlotinib (n = 150) or docetaxel (n = 151). The treatment groups were well matched for baseline characteristics including age, sex, PS, histology and smoking history. Median age was 68 years in the erlotinib group and 67 years in the docetaxel group. The majority of patients in each group were male (72% and 71%, respectively) and most patients in each group were current/previous smokers (74% and 76%, respectively) with 26% and 25%, respectively being non-smokers.

At the cut-off for the primary analysis, median PFS for Tarceva versus docetaxel was 2.0 vs 3.2 months (HR = 1.22 [95% CI: 0.97, 1.55]) and median OS was 14.8 versus 12.2 months, respectively (HR = 0.91 [95% CI: 0.68, 1.22]).

EGFR mutation status was determined in 255 (84.7%) of the 301 enrolled patients, including 199 patients with EGFR wild-type and 51 patients with EGFR mut+ve NSCLC. In the pre-specified secondary efficacy endpoint analysis of the subgroup of 199 patients with EGFR wild-type tumours, (109 of whom received erlotinib and 90 who received docetaxel), there was no significant difference between the erlotinib and docetaxel groups regarding baseline characteristics (sex, age, PS, histology, stage and smoking status).

Median PFS was reported as 1.3 months (95% CI: 1.1, 2.0) in the erlotinib group and 2.9 months (95% CI: 2.1, 3.3) in the docetaxel group (HR = 1.45 [95% CI: 1.09, 1.94]; p = 0.01) (Figure 10,

upper panel). A supportive Cox analysis with stratification factors confirmed the significant difference (adjusted HR = 1.57 [95% CI: 1.18, 2.11]; p < 0.01).

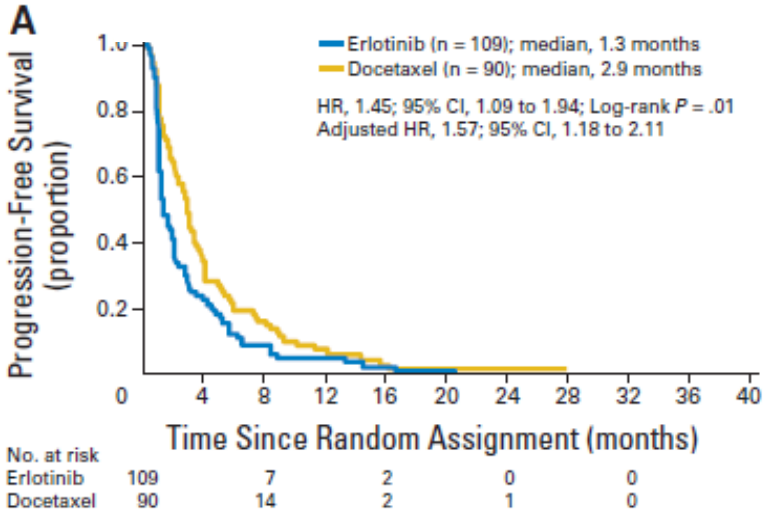
However, there was no difference in OS between the erlotinib and docetaxel treatment arms (Figure 10, lower panel). The median OS was 9.0 months (95% CI: 7.8, 14.5) in the erlotinib group and 10.1 months (95% CI: 7.3, 12.4) in the docetaxel group (HR = 0.98 (95% CI: 0.69, 1.39; p = 0.91). In terms of tumor response, 6 patients (5.6%) responded to erlotinib and 17 patients (20.0%) responded to docetaxel (p < 0.01).

In this study, further-line treatment following disease progression was given at the discretion of the physician and patient, and cross-over treatment was allowed. The number of patients who received further treatment was similar in the two groups (p = 0.22). Sixty-one patients (42.3%) who failed second-line treatment with erlotinib received docetaxel and 55 patients (37.9%) who failed second-line docetaxel received EGFR-TKIs. Patients with EGFR wild-type tumours who were treated with docetaxel and did not receive subsequent therapy had a trend toward longer OS when compared with patients treated with erlotinib (HR = 1.79; 95% CI 0.95, 3.35; p = 0.06). However, no significant difference in OS was seen between the erlotinib and docetaxel arms in patients who received any subsequent treatment (HR = 0.91; 95% CI 0.63, 1.32; p = 0.62).

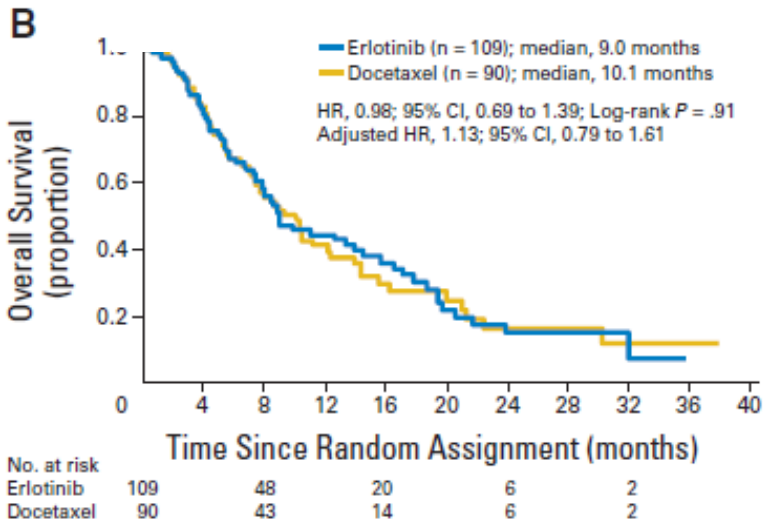
The results of this study in an EGFR-unselected population showed a small treatment benefit with respect to PFS for patients treated with docetaxel. However, there was no difference between erlotinib and docetaxel with respect to OS.

Figure 10: Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in the subpopulation of NSCLC patients with EGFR wild-type in the DELTA study

PFS



OS



Source: Kawaguchi et al. 2014

CHMP comment

This was a study conducted in Japan evaluating the efficacy of erlotinib vs. docetaxel in the second-line setting. Analysis of PFS and OS were conducted prospectively in WT-EGFRwt and EGFRmut as secondary endpoints. The mutation status was determined in 255 patients of which 199 were WT-EGFR. Median PFS was significantly longer in the docetaxel arm; 1.3 months (95% CI: 1.1, 2.0) in the erlotinib group and 2.9 months (95% CI: 2.1, 3.3) in the docetaxel group (HR = 1.45 [95% CI: 1.09, 1.94]; p = 0.01). However, median OS was 9 months in the erlotinib arm vs. 10.1 months in the docetaxel arm. This difference was not statistically significant (HR = 0.98 (95% CI: 0.69, 1.39; p = 0.91). Visual inspection of the KM curves reveal that there is no difference between the two treatment arms.

PROSE study

The **PROSE study** was a biomarker-stratified, randomized Phase 3 study conducted at 14 centres in Italy in patients aged > 18 years of age with stage IIIB or IV NSCLC who had progressed on or were refractory to one previous platinum-based chemotherapy regimen [Gregorc et al. 2014a]. Patients were randomized 1:1 to receive either erlotinib or chemotherapy (pemetrexed or docetaxel). Randomization was stratified by ECOG PS (0-1, or 2), smoking history (never, former or current smoker), center, and masked pretreatment serum protein test classification (poor or good). Patients received erlotinib (150 mg/day) or up to six cycles of pemetrexed 500 mg/m² every 21 days, or docetaxel 75 mg/m² every 21 days, according to the investigators' choice until disease progression, unacceptable toxicity, death, or withdrawal of consent. The primary endpoint was OS and secondary endpoints included PFS and objective response rate. Survival curves were calculated using Kaplan-Meier methodology and the difference between groups in time to event analysis was assessed with Cox proportional HRs, 95% CI, and p-values.

Of the 263 patients randomized, 129 patients received treatment with chemotherapy (docetaxel [n = 74], pemetrexed [n = 55]) and 134 patients received treatment with erlotinib. The treatment groups were balanced for clinical characteristics at baseline with the exception of histology where the erlotinib group had more patients with squamous cell carcinoma than the chemotherapy group (23% versus 12%, respectively). Median age was 64 years in the erlotinib group and 66 years in the docetaxel group. The majority of patients in each group were male (71% and 74%, respectively) and most patients in each group were former or current smokers (87% and 84% in the erlotinib and chemotherapy groups, respectively) with 13% and 16%, respectively being non-smokers. A proteomic test classification of good was associated with ECOG PS 0-1 (p = 0.002) and female sex (p = 0.007).

At the time of the primary analysis after a median follow up of 32.4 months [IQR 22.3 - 44.5 months], in the overall population, median OS was 9.0 months (95% CI: 6.8, 10.9) in the chemotherapy group and 7.7 months (95% CI: 5.9, 10.4) in the erlotinib group. The unadjusted HR was 1.14 (95% CI: 0.88, 1.49; p = 0.313) and when adjusted for stratification factors was 1.22 (95% CI: 0.93, 1.59; p = 0.148). PFS was not significantly different in the two treatment groups in the unadjusted analysis (HR = 1.27; 95% CI: 0.99, 1.62; p = 0.060) but was significantly better for chemotherapy-treated patients in the adjusted analysis (HR = 1.35; 95% CI: 1.05, 1.73; p = 0.02). A significant interaction between treatment and proteomic classification was noted both unadjusted and when adjusted for stratification factors. Patients with a proteomic test classification of 'poor' had worse survival on erlotinib than chemotherapy (HR = 1.72 [95% CI: 1.08, 2.74]; p = 0.022). There was no significant difference in OS between treatments for patients with a proteomic classification of 'good' (adjusted HR = 1.06 [95% CI: 0.77, 1.46]; p = 0.714).

Further-line treatment following disease progression was provided at the discretion of the investigator. Of the 129 patients in the chemotherapy group, 34 (26%) received erlotinib in the third line, and 65/134 patients (49%) in the erlotinib group received third-line chemotherapy.

EGFR mutation status was determined in 177 patients (67%) of whom 90 patients received chemotherapy and 87 patients received erlotinib. In a subgroup analysis performed in the 163 patients with confirmed EGFR wild-type tumors (84 chemotherapy, 79 erlotinib), median PFS was shown to be 4.3 months (95% CI: 2.3, 5.3) in the chemotherapy group and 2.2 months (95% CI: 1.9, 2.5) in the erlotinib group (Figure 11, upper panel) [Gregorc et al. 2014b].

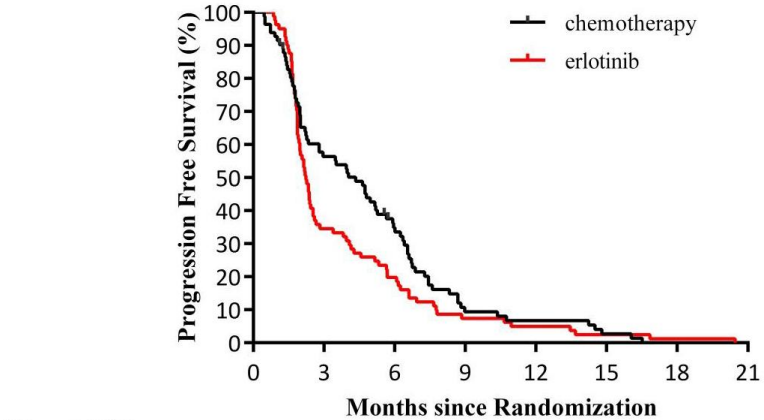
In this subgroup, median OS was 9.0 months (95% CI: 6.2, 10.9) in the chemotherapy group and 9.3 months (95% CI: 6.3, 11.6) in the erlotinib group (Figure 11, lower panel).There was no

significant difference between treatments in the unadjusted analysis for either OS (HR = 1.05 [95% CI: 0.75, 1.47]; p = 0.757) or PFS (HR = 1.28 [95% CI: 0.94, 1.76]; p = 0.121). Similarly, in the analysis adjusted for stratification factors, no significant difference between treatment was observed for OS (HR = 1.29; 95% CI: 0.91, 1.82; p = 0.159) or PFS (HR = 1.35; 95% CI: 0.98, 1.85; p = 0.067).

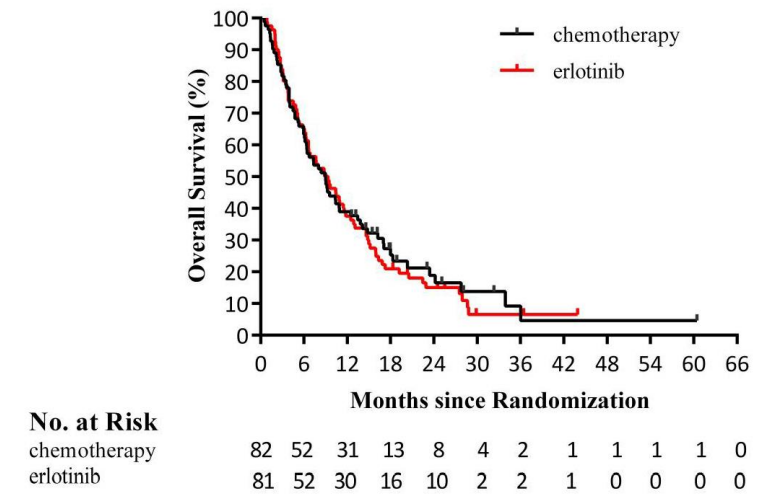
In the subgroup of NSCLC patients with EGFR wild-type in this study, chemotherapy showed a numerical improvement over erlotinib with respect to median PFS, although the difference was not statistically significant. No differences were observed between erlotinib and chemotherapy with respect to OS.

Figure 11: Kaplan-Meier curves of PFS (upper panel) and OS (lower panel) in the subpopulation of NSCLC patients with EGFR wild-type in the PROSE study

PFS



OS



Source: Gregorc et al. 2012

CHMP comment

This study randomised patients to erlotinib or docetaxel/pemetrexed. EGFR status was determined in 177 patients of which 163 were EGFRwt. As in the TITAN study, median PFS was shorter in the erlotinib arm, but, median OS was 9.0 months in the erlotinib arm compared to 9.3 months in the

chemotherapy arm (HR = 1.05 [95% CI: 0.75, 1.47]; p = 0.757). These results seem to show no detrimental effect of erlotinib on OS compared to chemotherapy in EGFRwt in the second-line setting.

HORG study

The **HORG (Hellenic Oncology Research Group) study** was a randomized, open-label, multicentre, phase 3 superiority study comparing the effect of pemetrexed versus erlotinib in pretreated patients with advanced (stage IIIB or IV) NSCLC who had progressed after first- or second line treatment [Karampeazis et al. 2013]. Patients were centrally randomized 1:1 to receive treatment with either pemetrexed (500 mg/m^2 Q3W) or erlotinib (150 mg/day) until disease progression, unacceptable toxicity or withdrawal of consent. Crossover between treatment arms was allowed on disease progression at the physician's discretion.

Randomization was stratified according to PS, disease stage, age (<65 versus ☐ 65), and response to first-line treatment. The primary endpoint was time to progression and secondary endpoints included PFS, OS, ORR and safety. Probability of survival was estimated using Kaplan-Meier methodology, and differences were tested using the log-rank test. Cox regression was used for multivariate and univariate analysis for and evaluation of the effects of covariates on TTP and OS. Mutational analysis was performed using DNA extracted from micro-dissected tissue samples. Exons 18-21 of the EGFR gene were amplified by PCR using nested primers, and then subjected to bidirectional automatic sequencing.

Of 357 patients enrolled into the study, 332 patients received treatment with either pemetrexed (n = 166) or erlotinib (n = 166). The treatment groups were balanced for clinical characteristics at baseline. Median age was 66 years in the pemetrexed group and 65 years in the erlotinib group. The majority of patients in each group were male (83% and 81%, respectively) and most patients in each group were active/ex-smokers (77% and 75%, respectively) with 15% and 18%, respectively being never smokers.

After a median follow-up of 27.3 months in the pemetrexed group and 29.0 months in the erlotinib group, in the overall population, there was no statistically significant difference in terms of TTP (p = 0.195), objective response rate (p = 0.469) or OS (p = 0.986) between the two treatment arms.

Thirty two patients (19.2%) crossed over from pemetrexed to erlotinib, and 7 patients (4.2%) were crossed over from erlotinib to pemetrexed following disease progression.

EGFR mutational status was assessed in 123/332 (37%) treated patients (62 pemetrexed; 61 erlotinib) who had adequate tumor tissue samples available. A subgroup analysis of 112 patients with confirmed EGFR wild-type tumors showed no significant difference in the primary efficacy endpoint of TTP between the erlotinib (n = 55) and pemetrexed (n = 57) arms with a HR = 0.92 (95% CI: 0.61, 1.38); median TTP in the erlotinib group was 2.9 months (95% CI: 1.7, 4.2). Similarly, there was no difference in OS between the two treatment arms (HR = 1.19; 95% CI: 0.77, 1.84); median OS in the erlotinib group was 9.7 months (6.4, 12.9). Median TTP and OS were not reported for the pemetrexed arm.

The authors concluded that both pemetrexed and erlotinib showed comparable efficacy in this population of pre-treated patients with metastatic NSCLC.

CHMP comment:

The data presented in the publication of the HORG study are minimal (Median TTP and OS for pemetrexed not reported). This makes it difficult to draw a proper conclusion on the efficacy of erlotinib in comparison to chemotherapy in this study.

Meta-analyses of Studies of Erlotinib versus Chemotherapy in Second- and Further Line Treatment of NSCLC Patients with EGFR wild-type Tumors

Two meta-analyses have been published to compare either erlotinib or gefitinib versus chemotherapy in second- and subsequent line therapy in EGFR wild-type patients. Zhao et al. [2014] conducted a systematic review of phase 2/3 prospective, randomized, controlled clinical trials involving histologically confirmed stage IIIB/IV NSCLC patients who were prospectively selected for EGFR wild-type genotype, or had EGFR wild-type status retrospectively identified and analyzed as a subgroup. Within this review, a meta-analysis of three large trials (TITAN, DELTA, and TAILOR) comparing erlotinib with chemotherapy (docetaxel or pemetrexed) showed no difference in OS between patients treated with erlotinib and those treated with chemotherapy (HR = 1.02 [95% CI: 0.83, 1.26]) and a PFS hazard ratio in favour of chemotherapy (HR = 1.37 [95% CI: 1.20, 1.56]) (Table 3; Figure 12).

In addition, Vale et al. [2015] performed a systematic review of studies of EGFR TKIs versus chemotherapy as second line therapy after first line chemotherapy in patients with EGFR wild-type tumours and patients with tumours harbouring EGFR-activating mutations. Meta-analysis data from 9 trials of patients with EGFR wild-type (including the trials evaluated by Zhao et al. 2014 and additionally V-15-32 [Maruyama et al. 2008], Li et al. [2014] and PROSE [Gregorc et al. 2014) showed no evidence of a difference between the effect of TKIs or chemotherapy on OS with a HR = 1.06 (95% CI: 0.93, 1.22). Although a PFS hazard ratio of 1.31 (95% CI: 1.16, 1.48) in favour of chemotherapy was shown, the authors did acknowledge inconsistency between the trial results, which might reflect the clinically heterogeneous nature of patients in the second line setting. The majority of trials included in the meta-analysis allowed treatment crossover upon progression. In light of this crossover, evidence suggests the sequence of chemotherapy followed by TKI or TKI followed by chemotherapy has similar survival.

Table 3 Comparison of OS estimates for Erlotinib versus Chemotherapy in Meta-analyses of Second and Subsequent-Line Therapy in EGFR wild-type Patients

Study	Analysis Set	Treatment	N	Median OS (months)	HR (95% CI)		Subsequent Therapy (All Subjects)
TITAN [Ciuleanu et al, 2012]	Subset	Erlotinib	75	6.6	0.85 (0.59, 1.22)		20% Pem 20% Doc
		Doc/Pem	74	4.4			20% erlotinib
TAILOR [Garassino et al, 2013]	All	Erlotinib	110	5.4	1.28 (0.89, 1.84)		6% Doc
		Docetaxel	109	8.2			4% Erlotnib
DELTA [Kawaguchi et al, 2014]	Subset	Erlotinib	109	9.0	0.98 (0.69, 1.39)		42.3% Doc
		Docetaxel	90	10.1			37.9% EGFR TKI
Meta-analysis of the above [Zhao et al, 2014]	Erlotinib vs. chemotherapy				1.02 (0.83, 1.26)		NR
Meta-analysis of 9 Phase 2/3 trials [Vale et al, 2015]	Erlotinib or gefitinib vs. chemotherapy		1400	NR	1.06 (0.93, 1.22)		NR

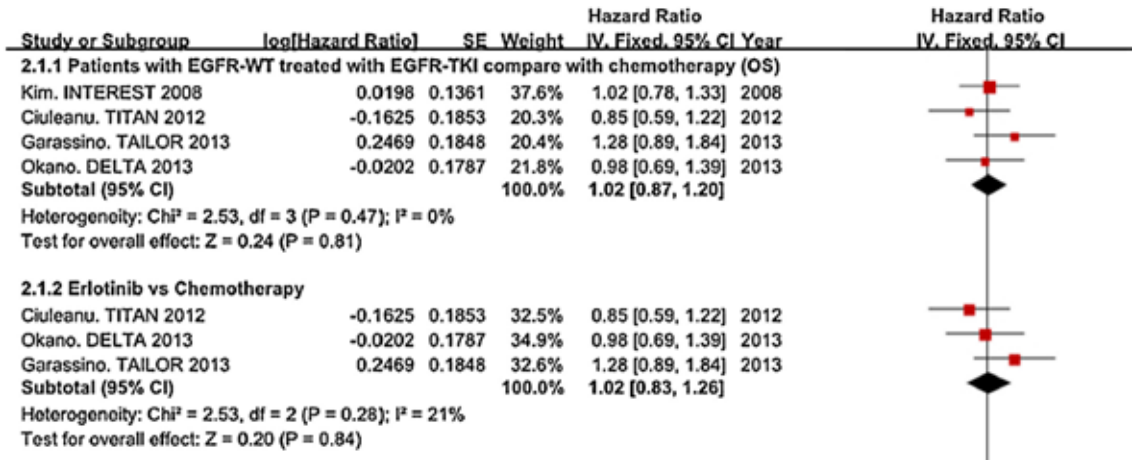
NR: Not reported; Pem: Pemetrexed; Doc: Docetaxel.

Table 4: Demographic and baseline characteristics for studies in NSCLC patients with known EGFR status included in meta-analyses by Zhao et al. 2014 and Vale et al. 2015.

Study	N	TKI	Control	Median Age (Range)	Sex: Male/ Female (%)	PS: 0-1 / 2 (%)	Current/ Former Smokers versus Never Smokers (%)	Histology: Adenocarcinoma (%)	EGFRwt: n (% of known)
Li et al.†	123	erlotinib	pemetrexed	54.5 (30-75)	64/36	94/6	74/26	100%	123/123 (100%)
TAILOR*†	219	erlotinib	docetaxel	66.5 (35-83)	69/31	91/9	78/22	68%	219/219 (100%)
TITAN*†	424	erlotinib	docetaxel / pemetrexed	59 (22-79)	76/24	80/20	83/17	50%	149/160 (93%)
PROSE†	263	erlotinib	docetaxel / pemetrexed	65 (33-85)	73/27	94/6	86/14	88%	163/177 (92%)
DELTA*†	301	erlotinib	docetaxel	67.5 (31-85)	71/29	96/4	75/25	69%	199/255 (78%)
INTEREST*†	1466	gefitinib	docetaxel	60.5 (20-84)	65/35	88/12	80/20	54%	229/267 (86%)
KCSG-LU08-01*†	135	gefitinib	pemetrexed	61 (30-78)	15/85	91/9	100/0	100%	38/71 (54%)
CTONG 0806*†	157	gefitinib	pemetrexed	56.5 (24-78)	64/36	100/0	51/49	96%	157/157 (100%)
V-15-32†	489	gefitinib	docetaxel	n/a	62/38	96/4	64/32	78%	26/57 (45%)

EGFR = epidermal growth factor receptor; PS = Performance Status; TKI = tyrosine kinase inhibitor; wt = wild-type.
* Studies included in the Zhao et al. 2014 meta-analysis
† Studies included in the Vale et al. 2015 meta-analysis

Figure 12: Comparison of OS with EGFR TKI vs. Chemotherapy in the Second-Line Setting



TITAN, TAILOR and DELTA: EGFR TKI was erlotinib. INTEREST: EGFR TKI was gefitinib.

In summary, while many trials have been conducted to investigate the effect of erlotinib versus chemotherapy both in NSCLC unselected patient populations and in EGFR wild-type subpopulations who have progressed following one or more courses of chemotherapy, none has shown convincing, statistically significant evidence to support superior efficacy of chemotherapy over erlotinib in the second- and further line treatment of NSCLC in EGFR wild-type patients. Furthermore, systematic reviews of recently reported Phase 2 or 3 trials in the second- and subsequent line treatment settings that either prospectively selected patients with EGFR wild-type status or retrospectively analyzed the EGFR wild-type subgroup have been published showing no statistical difference between chemotherapy and erlotinib with respect to OS, although a trend in favor of chemotherapy for PFS was seen.

CHMP comment:

Comparing all the data from the presented studies so far and the meta-analyses included no consistent conclusion can be drawn on the treatment of WT EGFR tumours with erlotinib in second- or further-line treatment. There is a significant benefit for chemotherapy with regard to PFS shown in the TAILOR and DELTA study and a trend toward chemotherapy is seen in TITAN and PROSE studies. For OS, only the TAILOR study shows a significant benefit for chemotherapy over erlotinib (but the results of the TAILOR study have to be interpreted with caution as mentioned above). No study reports a clear beneficial effect for erlotinib over chemotherapy.

Quote from the Vale meta-analysis: "Chemotherapy should be standard second-line treatment for patients with advanced NSCLC and wild-type EGFR. TKIs might be unsuitable for unselected patients. TKIs appear to benefit all patients compared with no active treatment as maintenance treatment, however, direct comparison with chemotherapy are needed."

It should be noted that in the studies performed with erlotinib different tests for mutational analysis were used. Furthermore, tumour DNA content of the used samples is not described in these studies.

Table: Overview on the methods used to detect EGFR mutation.

	BR.21	Li et al.	TAILOR	TITAN	HORG	DELTA	PROSE	ESCAP	BIOMAR
ARMS	x	x	x						
PCR-RFLP	x		x						
Sanger Seq.			x	x					
PCR-based bidirect. seq				x	x				
PCR-based (invader, peptide nuclear acid-locked PCR clamp, cycleave						x			
Not reported							x	x	x

Real World Data Analyses Demonstrating the Efficacy of Erlotinib in Second- and Further-line Treatment of NSCLC Patients

Additional supportive evidence demonstrating the efficacy of erlotinib in second- or further line therapy in EGFR wild-type patients in clinical practice is provided by real world data analyses of two French registry databases. Disease and treatment characteristics were also described in one German registry database. These real world data analyses have been performed by the MAH.

ESCAP-2011-CPHG Cohort Study

Study Design

The ESCAP-2011-CPHG is a prospective, national, multicenter, non-interventional cohort in France sponsored by the French College of Respiratory Physicians from General Hospitals (Collège des Pneumologues des Hôpitaux Généraux, CPHG). The ESCAP cohort was aimed at monitoring the therapeutic strategies implemented during the 2-year period following the diagnosis of primary lung cancer. Patients were included in ESCAP-2011-CPHG if the patient was included in the KBP-2010-CPHG cohort (requiring that the patient be at least 18 years of age, diagnosed between January 01 and December 31, 2010, and managed by Hôpitaux Généraux pulmonologist), managed by a center agreeing to participate in ESCAP-2011-CPHG, and provided oral consent to participate in ESCAP-2011-CPHG. The ESCAP-2011-CPHG cohort included 3943 patients. The present analysis included patients ≥ 18 years of age with locally advanced or metastatic NSCLC, without EGFR mutations, who were not participating in a clinical trial, who were treated with first line platinum-based chemotherapy, and who received a second or third line therapy with erlotinib or best supportive care (BSC).

The primary objective of this database analysis was to assess in real-life conditions the overall survival of EGFR wild-type patients treated with second- or third-line erlotinib for inoperable advanced or metastatic NSCLC.

The secondary objectives were to assess the overall survival of patients with second- or third-line best supportive care, to describe patients' characteristics according to second- or third-line therapy (with erlotinib or with best supportive care), and to search for predictive factors of survival of erlotinib-treated patients.

Results

Study Population

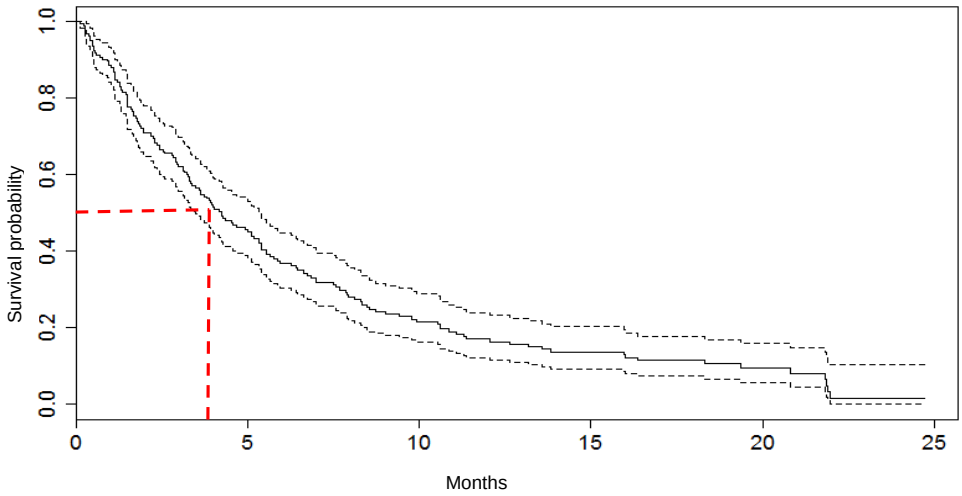
Two hundred and seventy four patients were analysed. Among these patients, 185 patients (68%) were treated with erlotinib [2L: n = 121 (65%); 3L: n = 64 (35%)], and 89 patients (32%) received BSC [2L: n = 62 (70%); 3L: n = 27 (30%)]. The majority of the 274 analysed patients were men (74%), less than 65 years old (60%), current or former smokers (88%), with more advanced disease (stage IV: 84%), and in good general condition (ECOG PS ≤1: 83%). This proportion of patients in a good general condition was higher in the erlotinib group (89% [95% CI: 83, 93]) than in the BSC group (72% [95% CI: 61, 81]). Disease characteristics between patients who received erlotinib and BSC patients were not significantly different.

At initial diagnosis of primary lung cancer, most patients had advanced disease stage (stage IV: 84%). Adenocarcinoma was the most frequent histology type of cancer (89%) and 6% of the patients presented with recurrent disease, without differences between treatment groups.

Overall survival in NSCLC patients with EGFR wild-type tumours treated with second- and third-line erlotinib

The median OS (Kaplan-Meier method) of patients treated with erlotinib as second- or third-line therapy was 4.2 months (95% CI; 3.5, 5.4) from treatment initiation until the end of patients' follow-up (Figure 13). The 3, 6, and 12 month survival rates were 62% (95% CI; 56, 70), 37% (95% CI; 30, 45), and 17% (95% CI; 12, 24), respectively.

Figure 13 Kaplan-Meier curve for overall survival in NSCLC patients with EGFR wild-type receiving second- and third-line erlotinib in the ESCAP-2011-CPHG cohort study

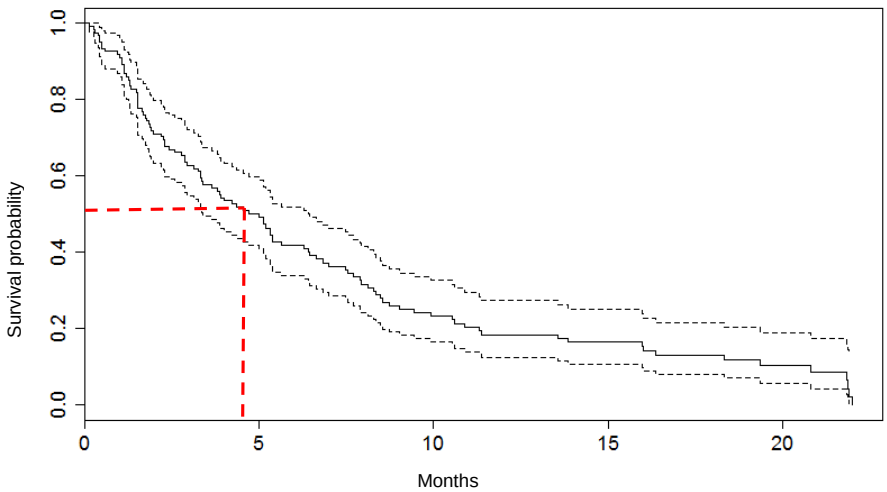


Among patients treated with second-line erlotinib only, median OS was 4.7 months (95% CI: 3.4, 6.4) and the 3, 6, and 12 month survival rates were 63% (95% CI; 55, 72), 42% (95% CI; 34, 52), and 18% (95% CI; 12, 27), respectively (Figure 14, upper panel). Sensitivity analyses using inverse probability weighting to adjust for age, gender, smoking status, ECOG PS class, tumor-node-metastasis (TNM) classification and cancer stage, histology, recurrent disease, and 1L chemotherapy (platinum salts, 3rd generation chemotherapy, derived platinum doublets, reason for treatment discontinuation), corroborated these OS estimates.

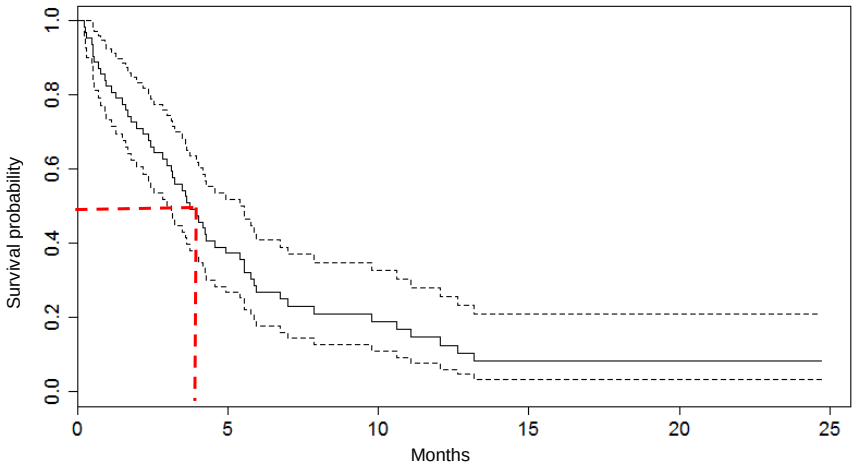
In patients treated with third-line erlotinib only, median OS was 3.7 months (95% CI; 3.1, 5.6) (Figure 14, lower panel). At 3, 6, and 12 months after the first intake of erlotinib, survival rates were 61% (95% CI; 50, 75), 27% (95% CI; 18, 41), and 15% (95% CI; 8, 28), respectively.

Figure 14 Kaplan-Meier curve for overall survival in NSCLC patients with EGFR wild-type receiving second-line (upper panel) or third-line (lower panel) erlotinib in the ESCAP-2011-CPHG cohort study

Second-line erlotinib



Third-line erlotinib



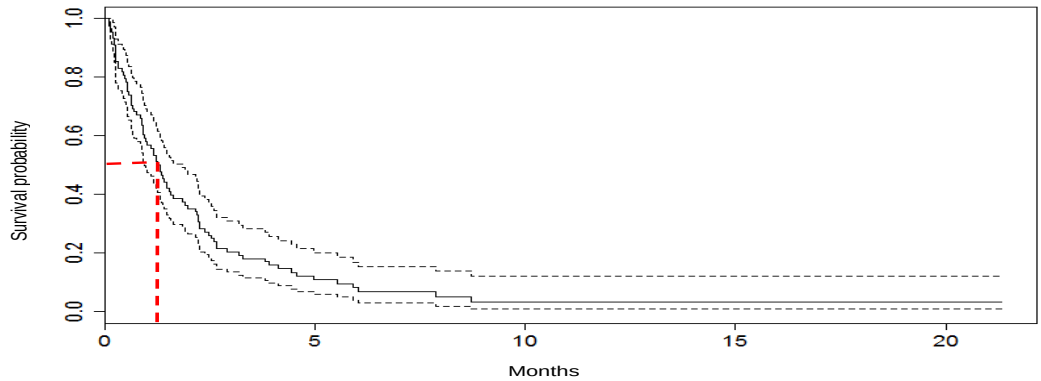
Overall survival in NSCLC patients with EGFR wild-type tumors treated with best supportive care

Median OS in patients receiving best supportive care was 1.3 months (95% CI; 1, 1.8), which was estimated from 88 patients without missing data from treatment initiation until the end of follow-up (Figure 15). At 3, 6, and 12 months after the first supportive care, survival rates were 20% (95% CI; 14, 31), 8% (95% CI; 4, 17), and 3% (95% CI; 1, 12), respectively.

Among patients who received only second-line best supportive care, median OS was 1.1 months (95% CI; 0.8, 1.8), estimated from 61 patients without missing dates. The 3, 6, and 12 month survival rates were 20% (95% CI; 12, 33), 8% (95% CI; 3, 19), and 4% (95% CI; 1, 15), respectively. The results were corroborated by sensitivity analyses using inverse probability weighting to adjust for age, gender, smoking status, ECOG PS class, TNM classification and cancer stage, histology, recurrent disease, and 1L chemotherapy (platinum salts, 3rd generation chemotherapy, derived platinum doublets, reason for treatment discontinuation).

Median OS among the 27 patients treated with third-line best supportive care was 1.5 months (95% CI; 1.2, 2.4). The 3 and 6 month survival rates were 22% (95% CI; 11, 45) and 9% (95% CI; 3, 33), respectively.

Figure 15 Kaplan-Meier curve for overall survival in NSCLC patients with EGFR wild-type receiving second- and third-line best supportive care in the ESCAP-2011-CPHG cohort study



This analysis may be subject to selection bias and confounding. Additionally, there was a lack of EGFR status documentation in a high proportion of patients, which may limit the generalizability of these results to all such treated EGFRwt advanced NSCLC patients. Furthermore, the increase in median OS from 1.1 months in second line to 1.5 months in third line for the BSC group may be a result of the very limited number of patients in third-line treatment.

Conclusions

Notwithstanding the limitations stated above, the findings from the database analysis showed improved OS for erlotinib over BSC, specifically in EGFR wild-type patients in second- and third line treatment in a real-life setting.

BIOMARQUERS FRANCE Cohort Study

Study design

The **BIOMARQUEURS FRANCE** cohort is a prospective, national multicenter, non-interventional registry which was designed to collect data on cancer molecular genetics in order to contribute to the improvement of management of NSCLC patients. The cohort included clinical and biological data from 17825 NSCLC patients from 28 French molecular oncogenetics platforms between November 2011 and April 2013, with a 12-month follow-up.

A retrospective analysis was implemented to assess, in real-world conditions, the OS of a sub-population of the BIOMARQUEURS FRANCE cohort with EGFR wild-type and no ALK translocation, and who were treated with second-line EGFR-TKIs or chemotherapy (Note: the EGFR-TKI was considered to be erlotinib by default). Secondary objectives were to assess the OS of second-line chemotherapy (taxanes or pemetrexed)-treated patients, the PFS in erlotinib- and in chemotherapy-treated patients, to describe patients' characteristics according to second-line erlotinib or chemotherapy, to describe chemotherapy and erlotinib discontinuations due to toxicity, and to search for predictive factors of patients' survival according to treatment (erlotinib or chemotherapy).

Results

Study population

The study cohort included 1278 patients age $\geq$ 18 years with locally advanced or metastatic NSCLC confirmed by histology, without EGFR mutation or ALK translocation, and having received a 2nd line treatment with chemotherapy or EGFR-TKI after a 1st line therapy. The EGFR-TKI with marketing authorization reported in the BIOMARQUEURS FRANCE cohort was considered to be erlotinib by default. Among the 1278 eligible patients, 410 (32%) were treated with erlotinib while 868 (68%) received chemotherapy in the second line. The majority of analysed patients were men (68%) and median age of the patient population was 62 years (range: 30-91). Most of the patients were current or former smokers (87%) and they were in good general condition in most cases (ECOG PS 0-1: 75%).

Compared to chemotherapy, erlotinib tended to be prescribed particularly in patients who were never smokers (17% versus 9%), with more advanced disease stage (stage IV: 90% versus 82%), older age ($\geq$ 65 years: 47% versus 33%) and poorer general condition (ECOG PS $\leq$ 1: 73% versus 82%).

Sixty-nine percent of patients had received pemetrexed as previous first-line treatment. Discontinuation of this first-line treatment was more often due to disease progression than to toxicity (in 66% of the patients versus 10%). By comparison with patients treated with chemotherapy,

patients treated with EGFR-TKI discontinued first-line treatment due to toxicity more often than patients having received chemotherapy (13%, CI 95%=[10; 16] versus 8%, CI 95%=[6; 10]).

Overall survival

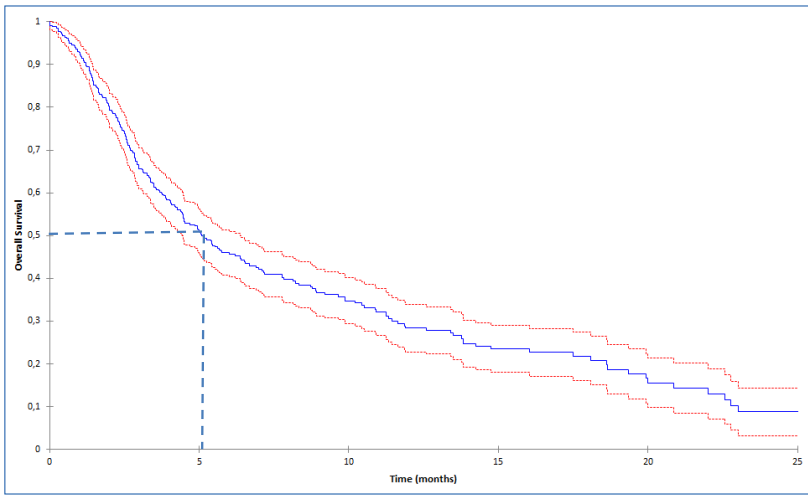
The median OS of patients treated with erlotinib was 5.1 months (95% CI: 4.4, 6.4) from the first disease progression after the first line treatment (

Figure 16, upper panel). At 3, 6, and 12 months, survival rates were 66% (95% CI: [61; 71]), 46% (95% CI: [41; 51]), and 28% (95% CI: [23; 34]), respectively.

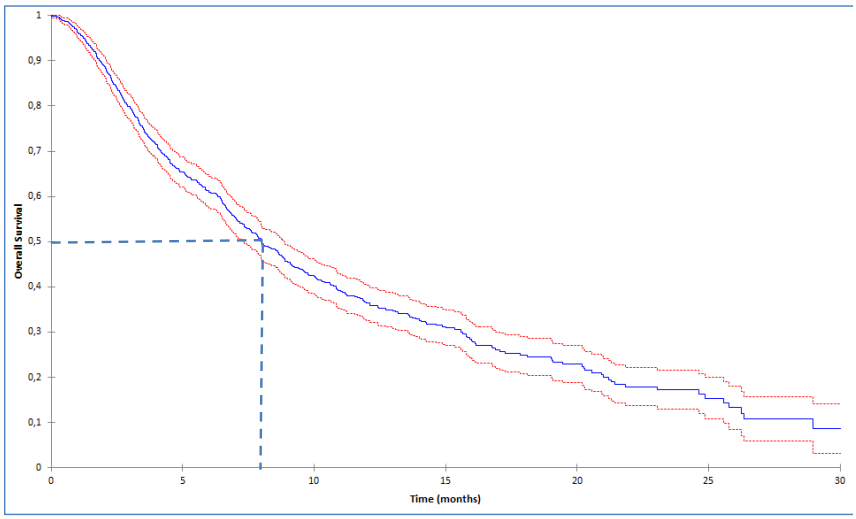
In patients treated with second-line chemotherapy, median OS was 8.0 months (95% CI: 7.3, 8.9) from first-line disease progression (16, lower panel). At 3, 6, and 12 months, survival rates were 80% (95% CI: 77, 82), 61% (95% CI: 58, 65), and 36% (95% CI: 33, 40), respectively.

Figure 16 Kaplan-Meier curve for overall survival in NSCLC patients with EGFR wild-type receiving second-line erlotinib (upper panel) or chemotherapy (lower panel) in the BIOMARQUEURS FRANCE study

Erlotinib



Chemotherapy



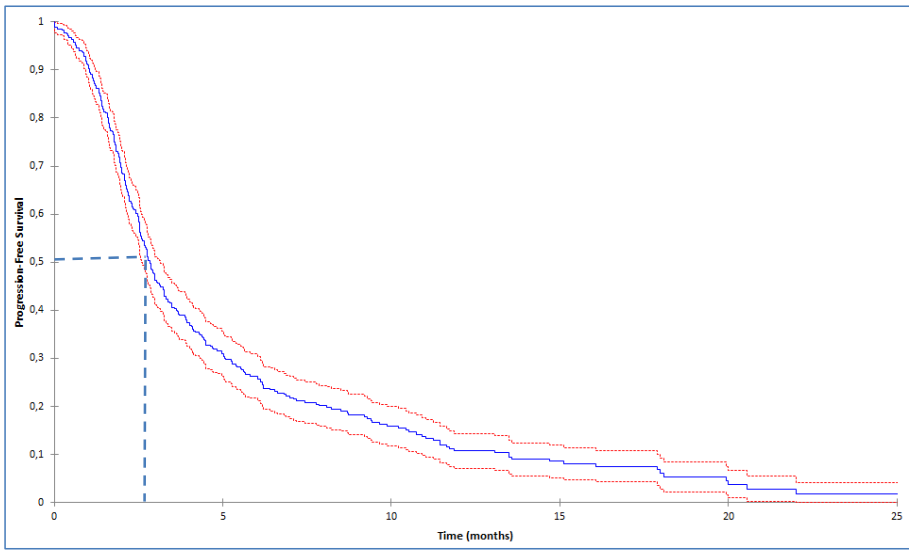
Progression-free survival

Median PFS in patients treated with second-line erlotinib was 2.8 months (95% CI: 2.6, 3.2) from first-line disease progression. At 3, 6, and 12 months, PFS rates were 46% (95% CI: 41, 51), 26% (95% CI: 22, 31), and 11% (95% CI: 7, 14), respectively (Figure 17, upper panel).

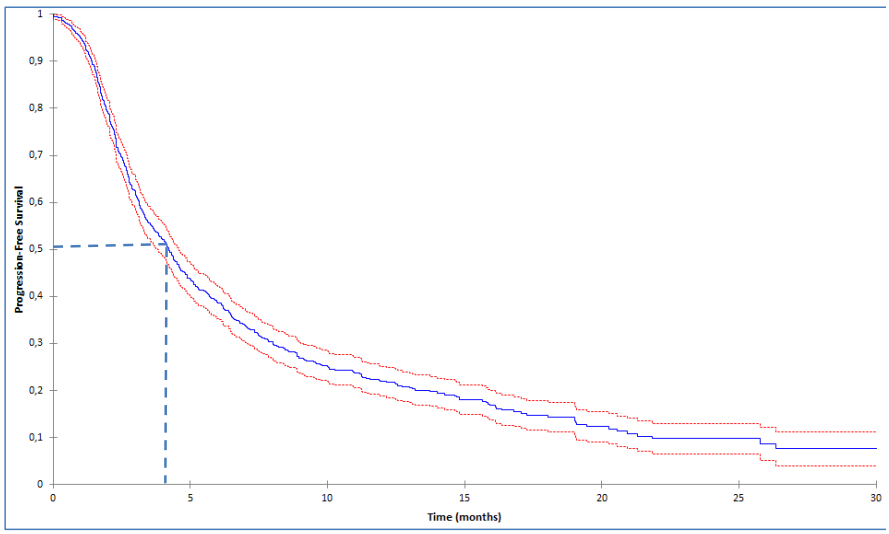
The unadjusted median PFS in patients treated with second-line chemotherapy was 4.2 months (95% CI: 3.8, 4.6) (Figure 17, lower panel). The 3, 6, and 12 month PFS rates were 62% (95% CI: [58; 65]), 39% (95% CI: [35; 42]), and 22% (95% CI: [19; 25]), respectively.

Figure 17 Kaplan-Meier curve for progression-free survival in NSCLC patients with EGFR wild-type receiving second-line erlotinib (upper panel) or chemotherapy (lower panel) in the BIOMARQUEURS FRANCE study

Erlotinib



Chemotherapy



These analyses using patients extracted from the BIOMARQUEURS FRANCE database have several limitations that may cause bias. For example, as the second line treatment initiation date was not collected in the cohort, the date of the first line disease progression was considered as the best estimate of the date of the initiation of second line therapy. The EGFR-TKI was considered to be erlotinib by default, although both gefitinib and erlotinib could have been used and gefitinib may not be as effective as a comparator against chemotherapy as erlotinib in second line therapy. In addition, patient selection bias may also have been introduced by excluding a high proportion of patients whose second line treatments were not documented. All covariates of interest for the choice of a specific second line treatment were not available in the database and were not taken into account for

sensitivity analyses. Furthermore, only patients starting a second line of treatment (and then experiencing disease progression) within a 12-month period after the genetic test request, could be included in the database analysis. These biases may limit the robustness and generalizability of these results to all such treated patients.

Conclusions

Although the results of this real-world database analysis demonstrate that chemotherapy shows a slight improvement in median PFS and median OS compared with erlotinib, the analysed patient population from the BIOMARKER FRANCE has several biases that may limit the generalizability of the study results. The OS difference is not yet clear when considering previous studies in similar patient populations. Nonetheless, erlotinib remains a valuable treatment option with a manageable safety profile in second- and further lines of therapy, particularly for those who may not tolerate further chemotherapy.

German TLK Lung Cancer Tumor Registry

The **German TLK Lung Cancer Tumor Registry** is a prospective, national, multicenter, non-interventional NSCLC registry. The TLK has recruited a representative sample of approximately 1.5% of patients newly diagnosed with NSCLC in Germany each year. It presents the course of the disease and treatment practice by oncologists in private practice and hospitals in Germany. The TLK covers a study period of six years (2010-2016), with a four-year recruitment phase (February 2010 to December 2014) and a two-year follow-up phase. By January 2016, 2434 patients recruited by 110 study sites from all over Germany were evaluable for analysis.

A retrospective analysis of a subcohort of the TLK registry was conducted to understand treatment utilization in the real world setting (Roche data on file). This analysis was based on eligible patients with locally advanced or metastatic NSCLC, age ≥18 years, without EGFR mutation, and who received a second- or further line treatment. In total 527 eligible patients (211 EGFR wild-type, 316 EGFR-untested) were analyzed (Table 5). Among these were 49 erlotinib users with EGFR wild-type and 69 erlotinib users with EGFR-untested status. Due to the limited sample size for erlotinib users in second-line, only disease and treatment characteristics were described. No statistically significant difference in patient and disease characteristics was observed among patients who received erlotinib, or docetaxel, or pemetrexed. Among EGFR wild-type patients, use of erlotinib was more common in third-line than second-line (17.2% versus 13.8%, respectively) while use of pemetrexed (18.3% versus 24.3%) or docetaxel (19.4% versus 30%) was less likely in third-line than second-line.

Although not directly related to treatment response, treatment utilization data observed from the TLK analysis were similar to findings from the real world studies using the two databases in France.

Table 5 Treatment Usage in Second- and Further Lines from the TLK Registry Analysis

Treatment Usage	2nd line N (%)		2nd line (and further lines) N (%)		3rd line N (%)	
Erlotinib usage						
Total	210	100%	211	100%	93	100%
Yes	29	13.8%	49	23.2%	16	17.2%
No	181	86.2%	162	76.8%	77	82.8%
Docetaxel usage						
Total	210	100%	211	100%	93	100%
Yes	51	24.3%	74	35.1%	17	18.3%
No	159	75.7%	137	64.9%	76	81.7%

Pemetrexed usage						
Total	210	100%	211	100%	93	100%
Yes	63	30.0%	84	39.8%	18	19.4%
No	147	70.0%	127	60.2%	75	80.6%

Source: TLK Registry Analysis

CHMP comment

The MAH presents additional evidence in the form of "real world data" to support the efficacy of erlotinib in the second line-setting in WT- EGFR patients. In the Biomarquers France study it is not possible to differentiate which EGFR-TKIs were used in the second-line. The MAH is assuming that it is erlotinib, however, this cannot be confirmed, and is a major drawback in this study.

The MAH also presents the results of a retrospective study conducted in Germany in WT-EGFR patients treated with +2L patients. This study showed erlotinib was more likely to be used in third-line than in second-line, while the opposite was the case for docetaxel and pemetrexed.

4.2.3. Discussion

In the first round, the MAH was requested to discuss the currently available evidence supporting the use of erlotinib in patients with locally advanced or metastatic NSCLC with WT-EGFR after failure of at least one prior chemotherapy regimen. The data presented in this variation include a new retrospective efficacy analysis of erlotinib in the subgroup of WT-EGFR patients enrolled in the pivotal BR.21 study and exploratory efficacy analysis of erlotinib in a clinically selected subgroup of patients (male, smoking patients with squamous histology), who are considered unlikely to harbour EGFR activating mutations. Furthermore, data from patient registry/study cohorts (e.g., ESCAP and BIOMARQUERS) were reported to assess the efficacy of erlotinib in WT-EGFR patients in a real-life condition. Several publications on the possible activity of erlotinib as second- and/or further line treatment of NSCLC patients with WT-EGFR tumours were also presented.

Mechanism of action in WT-EGFR patients

Erlotinib is a relatively selective reversible EGFR tyrosine kinase inhibitor. From a mechanistic point of view activity of the drug is expected in situations where prolonged activation of the EGFR receptor triggers tumor oncogenic activity through proliferation, invasion and metastasis, as it is the case of NSCLC patients harbouring EGFR activating mutations. The rationale supporting activity of Erlotinib in EGFR WT tumours is that EGFR signalling is able to drive tumor growth in the WT EGFR NSCLC. In this round, based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

BR.21 study, Erlotinib vs placebo

The MAH suggest that the role of erlotinib might differ between maintenance and second-line treatment and this might be due to differential EGFR expression in chemotherapy-sensitive (low EGFR expression) and chemotherapy-resistant cells (high EGFR expression). In this round additional pre-clinical evidence is presented to support this hypothesis. Unfortunately, no clinical evidence is presented to support this hypothesis.

In consequence to this hypothesis, The MAH suggests that activity of erlotinib in the EGFR WT NSCLC population could be due to high expression of WT EGFR resulting in an increased activation of the signalling cascade and subsequent tumour growth. EGFR expression level could also justify some

activity of erlotinib in NSCLC either squamous cell histology, as high EGFR gene copy-number and protein overexpression have been reported more frequently in tumour specimens with squamous cell compared with adenocarcinoma histology (82% versus 44%).

Erlotinib and other approved second- and further line treatment regimens

The main publications comparing erlotinib to chemotherapy (pemetrexed and docetaxel) are also discussed in this variation. They consist of a heterogeneous group of publications related to several studies performed in different populations, and/or in different treatment setting and/or employing different comparators. Interpretation of the results is also hampered in several studies due to the limited sample size and the fact that EGFR WT patients represented only subgroups of the population treated in the studies. Similarly, the publications related to real-life databases/patient registries present important limitations as discussed above. Importantly, different tests have been used in the different studies in to evaluate EGFR status.

Overall, conflicting results are presented in the literature, ranging from studies (e.g., TAILOR) clearly indicating superiority of chemotherapy vs erlotinib in terms of PFS and OS in EGFR WT patients and other trials/subgroup analyses suggesting no significant difference in OS when comparing chemotherapy to erlotinib (for TITAN, DELTA and PROSE trial). Of note, a numerical trend in median PFS favouring chemotherapy was identified in all these trials.

In this round, the applicant provided new data by means of two case studies. Both case studies point towards an effect of erlotinib in these WT-EGFR patients, However, two case studies are not considering as outstanding and related with uncertainties.

Conclusion

The IUNO study, which has been assessed in a previous variation, showed no benefit of early erlotinib treatment in patients with NSCLC without known EGFR activating mutations. In the EU, the IUNO study led to the revision of the maintenance indication and the benefit/risk balance in the second-line indication after failure of prior chemotherapy came into question, in particular for patients without EGFR mutation.

The benefit/risk balance of erlotinib in the 2nd-line and beyond treatment of patients with locally advanced or metastatic WT-EGFR NSCLC involves uncertainties for the following reasons:

First, the concerns persist on the interpretability of the currently presented clinical evidence to support erlotinib efficacy in comparison to both placebo as chemotherapy in WT-EGFR NSLCLC (e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests).

Second, it has been known for a long time that EGFR signalling is able to activate pathways related to tumour growth, however, based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

As a consequence, the MAH has proposed to reflect the uncertainties in relation to the 2nd-line and beyond NSCLC indication including the following wording in section 4.1 of the SmPC:

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated when other treatment options are not considered suitable.

The CHMP agrees to this revision of the indication.

4.3. Clinical Safety aspects

Erlotinib has a well-established and manageable safety profile. Important identified risks associated with erlotinib treatment include cutaneous toxicity, interstitial lung disease (ILD), liver injury, gastrointestinal fluid loss, gastrointestinal perforation, ocular toxicity, interaction with potent inducers and inhibitors of cytochrome P450 (CYP) 3A4, interaction with medicinal products that alter pH of the upper GI tract and interaction with smoking (CYP1A2 induction).

In contrast to currently approved chemotherapeutic agents, erlotinib is not associated with myelosuppression, neuropathy, or severe emesis. The lack of classical chemotherapy toxicity, the low rate of patient withdrawal, and the ease of administration make erlotinib a favorable and well-tolerated anti-cancer treatment option.

In the BR.21 phase III pivotal study of second line treatment of advanced NSCLC, the overall incidence of adverse events (AEs) regardless of causality was similar between the erlotinib and placebo arms (99% vs 96%, respectively). Rash (75%, vs 17% in the placebo group) and diarrhoea (54%, vs 18% in the placebo group) were the most common AEs regardless of causality in the erlotinib arm. Most were Grade 1 or 2 in severity (rash: 66% vs 17%; diarrhoea: 48% vs 17%) and manageable without intervention. Severe rash and diarrhoea occurred in 9% and 6%, respectively, in erlotinib-treated patients and each resulted in discontinuation in 1% of patients. Dose reductions were required for 10% of patients due to rash and 4% of patients due to diarrhoea.

Other common AEs, regardless of severity, that occurred more frequently in the erlotinib group versus the placebo group included nausea (33% vs 24%), vomiting (23% vs 19%), stomatitis (17% vs 3%) and conjunctivitis (12% vs 2%). These events were mainly mild to moderate in severity and infrequently resulted in dose modification. Overall, 27% of patients in the erlotinib group experienced eye disorders (including dry eyes and conjunctivitis) versus 9% in the placebo group. Most were mild in severity.

The most common serious adverse event (SAE) was dyspnea, reported for 13% of erlotinib-treated patients and 12% of patients in the placebo group. Six patients (4 erlotinib, 2 placebo) were classified as having ILD-like SAEs (i.e., a 0.8% incidence in each arm). More patients on erlotinib (7%) experienced pulmonary infections compared with the placebo arm (2%). These included pneumonia, sponsor-assessed probable pneumonia, lung or respiratory infection, and lung abscess. However, taking into account the longer survival time and time on treatment for erlotinib-treated patients, the incidence of infections per patient week was not different between the groups. The treatment effects on hematology and blood chemistry parameters were negligible.

In contrast to erlotinib, currently approved chemotherapeutic options for second- and further line treatment of NSCLC are associated with significant toxicity. For example, docetaxel monotherapy is associated with the following common events: neutropenia, anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia; in addition to hypersensitivity reactions (including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea and fever or chills), severe peripheral neurotoxicity, cutaneous reactions and fluid retention, including events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain.

Pemetrexed is associated with bone marrow suppression manifesting as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal (GI) toxicities, manifesting as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other notable undesirable effects associated with pemetrexed therapy include renal toxicities, increased aminotransferases,

alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy while rarely seen events include Stevens-Johnson syndrome and toxic epidermal necrolysis.

The most common adverse reactions associated with recently approved immunotherapeutic agents for treatment of NSCLC either alone or in combination include fatigue, rash, pruritus, diarrhoea, nausea and immune-related events. These include immune-related pneumonitis (including ILD), immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (such as hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism), immune-related rash, immune-related nephritis and renal dysfunction, and infusion-related reactions. These conditions can be managed with immunosuppressive doses of corticosteroids or other immunosuppressive therapy and treatment modifications.

CHMP comment

The safety profile of Erlotinib is considered to be well-established and manageable. The MAH indicates that it is not expected that the safety profile will differ for the subpopulation of NSCLC patients with WT EGFR tumours. This is acknowledged. Although the nature of the adverse events is different when comparing erlotinib and chemotherapy, the impact of the erlotinib safety profile on patients is expected to be at least similar to the impact of chemotherapy.

5. Request for supplementary information

General

Major Objection

1. Due to the results of the IUNO study (which led to the revision of the maintenance indication), the benefit/risk balance in the second-line indication in WT-EGFR tumours was, and is, called into question. The clinical evidence currently presented suggests a benefit of erlotinib over placebo, while the efficacy of erlotinib compared to chemotherapy remains inconclusive. In both cases the interpretability of the data is hampered (by e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests) and therefore the clinical efficacy of erlotinib in second- and further-line WT EGFR NSCLC remains questionable. In addition, due to the rapidly changing treatment landscape of NSCLC it is essential to pinpoint if, and if so, which patients with EGFR WT NSCLC truly benefit from the treatment with erlotinib (e.g. high EGFR expression). The information currently presented does not allow us to determine this patient population. Finally, the rationale supporting activity of Erlotinib in EGFR WT tumours, which is the fact that EGFR signalling must be able to drive tumour growth in WT EGFR NSCLC, is build on theoretical grounds. No (non-)clinical evidence is provided by the MAH on this rational specifically.

   Therefore, the benefit/risk balance is currently undetermined and the MAH is asked to provide and discuss the clinical evidence in order to support activity of erlotinib (and therefore a positive benefit/risk balance of erlotinib) as second and beyond line of treatment of NSCLC patients with EGFR WT status. The MAH is requested to included discussion, with both non-clinical and clinical evidence, on the concerns on the interpretability of the presented data, the patient population that is likely to benefit and the rational that EGFR signaling must the able to drive tumour growth in WT EGFR NSCLC.

Other Concerns

2. No clinical data are presented to justify the idea of Erlotinib inhibiting the IPP complex and EMT. Could the MAH discuss the available clinical data to confirm the hypothesis of Erlotinib inhibiting the IPP complex and subsequent EMT.
3. The MAH suggest that the difference between chemo-sensitive and chemo-resistant tumors is mainly based on the EGFR expression, which is higher in resistant cells. This would, in view of the MAH, constitute the rational supporting activity of erlotinib in EGFR WT NSCLC patients. However, the early switch maintenance therapy with erlotinib performed in the IUNO study, enrolling patients with high EGFR expressing levels, did not result in a better efficacy than with placebo. Therefore, "high" EGFR expression due to chemo-resistance cannot be the only reason for Erlotinib showing a benefit in second- and further-line treatment in EGFR WT NSCLC. The MAH should comment on this observed discrepancy.
4. The MAH suggest that no big difference can be detected between the OS of the second-line erlotinib and the second-line chemo in the IUNO study. This OS is calculated with the starting point at randomization. The MAH is requested to provide the PFS and OS with a starting point at first time PD, to see whether still no difference is found between chemotherapy and Erlotinib treatment (PFS2 and OS2).
5. In the BR.21 study only 233 of 328 samples were considered to be adequate for EGFR mutation analysis, of which in the end 204 could be tested for a EGFR mutation. The MAH is asked to elaborate on the criteria used to categorize a sample as adequate and to indicate why for 29 samples no proper mutational analysis was obtained.
6. In the BR.21 study the MAH should also present the EGFR expression level (as assessed by IHC) of patients with proper samples for mutational analysis.
7. The MAH is asked to provide data on EGFR expression level of the samples in the both the WT and squamous subgroup of the BR.21. Please provide the efficacy parameters (PFS and OS) for patients with low and high expression status in both the WT and squamous NSCLC subgroups.
8. The role of erlotinib might differ between maintenance and second-line treatment and this might be due to differential EGFR expression in chemotherapy-sensitive and a chemotherapy-resistant cells. The MAH is asked to perform subgroup analyses in the BR.21 study as a clinical argument for this hypothesis. Possible analysis that could be performed: Subgroup analysis (BR.21) on PFS and OS in patients have a response or stable disease during the chemotherapy vs. patient progressing during chemotherapy.

6. Assessment of the responses to the request for supplementary information

Question 1
Major Objection

Due to the results of the IUNO study (which led to the revision of the maintenance indication), the benefit/risk balance in the second-line indication in WT-EGFR tumours was, and is, called into question. The clinical evidence currently presented suggests a benefit of

erlotinib over placebo, while the efficacy of erlotinib compared to chemotherapy remains inconclusive. In both cases the interpretability of the data is hampered (by e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests) and therefore the clinical efficacy of erlotinib in second- and further-line WT EGFR NSCLC remains questionable. In addition, due to the rapidly changing treatment landscape of NSCLC it is essential to pinpoint if, and if so, which patients with EGFR WT NSCLC truly benefit from the treatment with erlotinib (e.g. high EGFR expression). The information currently presented does not allow us to determine this patient population. Finally, the rationale supporting activity of Erlotinib in EGFR WT tumours, which is the fact that EGFR signalling must be able to drive tumour growth in WT EGFR NSCLC, is build on theoretical grounds. No (non-)clinical evidence is provided by the MAH on this rational specifically.

Therefore, the benefit/risk balance is currently undetermined and the MAH is asked to provide and discuss the clinical evidence in order to support activity of erlotinib (and therefore a positive benefit/risk balance of erlotinib) as second and beyond line of treatment of NSCLC patients with EGFR WT status. The MAH is requested to included discussion, with both non-clinical and clinical evidence, on the concerns on the interpretability of the presented data, the patient population that is likely to benefit and the rational that EGFR signaling must the able to drive tumour growth in WT EGFR NSCLC.

Summary of the MAH's response

The objective of the IUNO study was to assess whether erlotinib administered as first-line (1L) maintenance therapy was associated with better clinical outcome than erlotinib administered at progression (2L treatment). Thus, the IUNO study (BO25460) only included patients who had disease control or were responding to treatment with 1L chemotherapy i.e. the inclusion criterion was as follows:

"Completion of four cycles of a permitted platinum-based chemotherapy without progression (i.e. CR, PR, or SD). *This Is A Mandatory Requirement For Study Entry*. A maximum interval of 28 days between the end of the last chemotherapy cycle and randomization will be allowed" [variation EMEA/H/C/000618/II/0043; TARCEVA® EPAR; IUNO CSR 1052824].

Thus, a direct comparison should not be made from the IUNO study to Study BR.21, which enrolled patients who had *failed* at least one line of chemotherapy and thus focusses on 2L and further lines of treatment. It is notable that in the IUNO study there was no discernable difference in efficacy between erlotinib and chemotherapy in the 2L phase of the study. If erlotinib had no efficacy at all in the 2L setting, one would have expected a difference in the OS in those patients who received 2L chemotherapy compared to those who received 2L erlotinib, but this was not evident. This is observational as the 2L portion of the study was not randomized and not designed or powered for a 2L analysis.

The MAH acknowledges that approval of erlotinib for treatment of NSCLC after failure of at least one chemotherapy regimen was based on the positive results from the pivotal BR.21 study, which did not specifically distinguish the population of patients with WT EGFR NSCLC. This is because the study was completed before EGFR mutation testing had been identified as a predictive biomarker [Lynch et al. 2004]. Nonetheless, the analyses on the totality of the data provided as part of this Type II variation are based on several data sets that look specifically at the effects of erlotinib in patients with WT EGFR status, both as subgroup analyses from the data of Study BR.21 and from other published studies. There are both preclinical and clinical studies (as presented below) that support the rationale that

EGFR signaling is able to drive tumor growth and that blocking EGFR activity can meaningfully inhibit tumor growth. Therefore, while the subgroup analyses of WT EGFR in isolation could be challenged in view of the retrospective nature and the small sample size, taken together, these data as discussed below, consistently support the conclusion of a modest but clinically relevant benefit of erlotinib in patients with locally advanced or metastatic NSCLC without EGFR-activating mutations after failure of at least one prior chemotherapy regimen. EGFR-activating mutations identify the patients who benefit the most from treatment with erlotinib, but patients without these mutations also benefit.

PRECLINICAL EVIDENCE OF THE RATIONALE FOR ERLOTINIB ACTIVITY IN WT EGFR TUMORS

The role of WT EGFR as an important driver of tumorigenicity has been well established in preclinical molecular studies. Tumors expressing mutant EGFR have been shown to have greater sensitivity to EGFR TKIs than tumors expressing WT EGFR, but inhibiting either type of EGFR can inhibit tumor growth. The magnitude of tumor cell inhibition by EGFR TKIs differs between WT and mutant EGFR forms and helps to explain the spectrum of clinical activity observed.

EGFR belongs to a family of structurally related receptor tyrosine kinases that play a critical role in many cell-signaling pathways that influence cell division, apoptosis, motility, and adhesion [Yarden 2001]. Activated EGFR initiates a signal transduction cascade that can culminate in the activation of genes that play a critical role in tumorigenesis, tumor growth, and tumor survival. Whereas normal cells have tightly controlled EGFR signaling [Arteaga 2002], abnormal activation (e.g. overexpression of EGFR or EGFR ligands) or dysregulation of EGFR (e.g. EGFR phosphorylation, EGFR dimerization) in normal cells can result in the tumorigenic phenotype [Salomon et al 1995; Kumar et al 1998]. Activation of EGFR signaling can result from mechanisms other than just activating mutations, such as invasion by viral oncogenes [Miller and Raab-Traub 1999] and in response to DNA damage caused by cytotoxic treatments [Lu et al. 2011]. As the studies below show, as tumor cells develop resistance to chemotherapies in certain tumor types, they increase EGFR expression as an adaptive response and develop increased sensitivity to EGFR inhibitors.

Early evidence that EGFR can drive tumorigenicity came from studies showing that known tumor-causing viruses encoded the EGFR proto-oncogene cellular homolog found in the avian erythroblastosis virus (AEV) v-erbB as well as other cancer-causing viruses. Cell culture studies found that conditioned media containing EGFR ligands can confer the transformed phenotype to normal cells and drive tumor cell lines to become more metastatic through the activation of WT EGFR [Todaro et al. 1980; Roberts 1980; Sporn and Todaro 1980; Todaro et al. 1981; Twardzik et al. 1985; Pike et al. 1982]. Subsequently, it was found that WT EGFR and its ligands are overexpressed or involved in autocrine growth loops in a number of tumor types, including NSCLC [Fujino et al. 1996; Rusch et al. 1997; Salomon et al. 1995]. Similarly, dysfunctional EGFR has been observed in many human cancers from colon, pancreatic, breast, ovary, bladder, kidney, gliomas, and lung [Arteaga 2002; Wells 1999]. In addition, overexpression and dysregulation of EGFR has been reported to be associated with poor prognosis, reduced survival, resistance to chemotherapy, and resistance to hormonal therapy [Arteaga 2003; Salomon et al. 1995; Chen et al. 2000; Wosikowski et al. 2000; Tørring et al. 2000; Woodburn 1999]. These data show that EGFR signaling is able to drive tumor growth in the WT EGFR NSCLC and other tumor types.

Conversely, inactivation of EGFR pathways can significantly inhibit tumorigenesis, tumor growth and tumor survival, which is the basis of the rationale for the activity of erlotinib in WT EGFR tumors. Erlotinib was shown to inhibit the autophosphorylation of the EGFR in a variety of EGFR over-expressing tumor cells, and to cause cell cycle arrest and apoptosis in multiple cell types [Moyer et al.

1997; Barbacci et al. 2003]. Other preclinical studies with erlotinib found that, in vivo, erlotinib selectively inhibits WT EGFR-specific tyrosine phosphorylation in human tumor xenografts (ED50 of 10 mg/kg p.o. when given as a single dose) with significant duration of action and that daily dosing substantially inhibits growth and results in regression of human tumor xenografts [Pollack et al. 1999]. Subsequent studies using in vitro cell culture and in vivo animal models have shown anti-tumor activity by EGFR tyrosine kinase inhibitors (TKIs) [Mendelsohn and Baselga 2006; Baselga 2002; Harari 2007; Arteaga 2002; Grünwald and Hidalgo 2003].

In a number of preclinical studies, tumor cells that were exposed to or developed resistance to chemotherapy or radiation were observed to upregulate expression of WT EGFR [Dai et al. 2005; Servidei at al. 2008; Naruse et al. 2002; Schmidt-Ullrich 1994; Zimmermann 2006; Kiyozuka 2013]. It was found that with upregulated WT EGFR, tumor molecular-subtypes were also more sensitive to erlotinib [Dai et al. 2005]. Although a subgroup of patients have been found to have a significantly higher response rate to EGFR TKIs due to the presence of specific mutant forms of EGFR (mtEGFR) in lung tumor biopsies, a number of other mutations have been identified in NSCLC patients that may be linked to poor responsiveness to EGFR TKIs (e.g. ALK, cMET). The identification of mutant proteins and signaling pathways that can bypass EGFR signaling [Tsao et al. 2016] and can be considered for other treatments may allow for enrichment of the WT EGFR NSCLC patients, for whom EGFR TKI's still offer a reasonable treatment option.

Although activating EGFR mutations increase the sensitivity of EGFR to erlotinib, WT EGFR is also inhibited by erlotinib [Dai et al. 2005]. Tumor cells can upregulate expression of WT EGFR in response to the damage caused by chemotherapy [Lu et al. 2011] and subsequently develop chemo-resistance [Hsu et al. 2009]. This increased expression contributes to greater WT EGFR activity and is believed to be one of the key reasons erlotinib exerts an inhibitory effect on certain chemo-resistant, progressing tumor cells. Thus, although there is no constitutive activation of EGFR signaling due to a mutation, there is increased presence of the EGFR, which can increase EGFR signaling in general and enhance activation of genes that play a role in tumor growth and survival.

In summary, WT EGFR is known to play an important role in the development, progression and survival of human epithelial malignancies and is a relevant target for antineoplastic therapies. Consistent with this, erlotinib has been shown to inhibit tumor growth due to its interaction with WT EGFR and this may be enhanced in chemotherapy-resistant tumors. Taken together, these preclinical studies provide evidence to support the rationale for the activity of erlotinib in chemotherapy-resistant WT EGFR tumors.

CLINICAL EVIDENCE FOR ERLOTINIB ACTIVITY IN PATIENTS WITH WT EGFR NSCLC

There are several clinical studies, including the BR.21 study, that assess the effect of erlotinib in patients with WT EGFR NSCLC, and all of these studies show that these patients derive modest but clinically relevant benefit from treatment with erlotinib after failure of previous chemotherapy.

Evidence from Study BR.21

The pivotal BR.21 study demonstrated a highly significant and clinically meaningful survival prolongation of erlotinib given as an oral therapy to 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Compared to placebo, erlotinib, as a single-agent, prolonged OS with a hazard ratio (HR) of 0.73 ($p = 0.001$) in favor of erlotinib (median OS of 6.7 months vs 4.7 months).

Patients treated with erlotinib had significantly improved quality of life parameters, with delayed symptomatic deterioration of cough, dyspnea and pain compared to patients receiving placebo. The median time to deterioration of cough was 28.1 weeks in the erlotinib arm compared to 15.7 weeks in the placebo arm, p = 0.041, HR 0.75 (95% CI, 0.56 – 1.00). For dyspnea, it was 20.4 weeks in the erlotinib arm compared to 12.1 weeks in the placebo arm, p = 0.031, HR 0.72 (95% CI, 0.56 – 0.93) and for pain it was 12.1 weeks in the erlotinib arm compared to 8.1 weeks with placebo p = 0.040, HR 0.77 (95% CI, 0.61 – 0.97). These symptom benefits could not be attributed to use of radiotherapy or concomitant medications.

The survival benefit from erlotinib was also seen in all pre-specified patient subgroups. The robustness of the survival benefit was assessed in various subset analyses that included the stratification factors at randomization and baseline. In addition, an exploratory survival analysis, excluding responding patients and patients who were not evaluable for response, showed that the median survival of the erlotinib patients was 7.4 months, compared with a median of 6.7 months in the placebo arm (HR = 0.82; p = 0.037). In patients who progressed rapidly after initiation of treatment, who were considered non-responders, there still appears to be an observed benefit. Thus, it appears that the overall results were not a consequence of a small group of patients who had considerable response.

The study enrolled a mixed population of NSCLC patients with WT EGFR and EGFR mutant tumors [Zhu et al. 2008]. Although the BR.21 study was completed before EGFR mutation testing became established practice, retrospective biomarker testing for EGFR was performed using tumor samples from 233 patients. An analysis was performed for which the WT EGFR subgroup was categorized as all patients excluding those whose tumors had exon 19 deletions and exon 21 L858R mutations [Zhu et al. 2008]. Another analysis used a more conservative approach that categorized the WT EGFR subgroup as all patients excluding those whose tumors had exon 19 deletions and exon 21 L858R mutations, and patients whose tumors had other indeterminate variants in EGFR.

The HRs for PFS and OS of the WT EGFR subgroup in the more conservative analysis, were similar to the full analysis set (FAS) population (Table 1). The analysis showed a numerically favorable OS in the WT EGFR subgroup with an unadjusted HR of 0.75 (95% CI: 0.52, 1.10; p = 0.1443) in favor of erlotinib, which was similar to the magnitude in the FAS (unadjusted HR = 0.76; 95% CI: 0.64, 0.91; p = 0.0018). A PFS benefit (unadjusted HR = 0.56; 95% CI: 0.39, 0.81; p = 0.0013) was observed for erlotinib compared with placebo in the WT EGFR subgroup, which was consistent with that seen in the FAS population (unadjusted HR = 0.64; 95% CI: 0.54, 0.75; p<0.0001) (Table 1). The WT EGFR subgroup also demonstrated a higher response rate in erlotinib-treated patients (5.9%; 95% CI: 2.2, 12.4) compared with placebo-treated patients (2.1%; 95% CI: 0.1, 11.1%) and the response rate was consistent with that observed in the erlotinib arm of the FAS (8.0%; 95% CI: 5.7, 10.8%). Thus, these data from Study BR.21 support the conclusion of clinical benefit for erlotinib in WT EGFR patients who had failed at least one line of chemotherapy.

Table 1 Study BR.21: Summary of Efficacy Results for FAS and WT EGFR Populations

	Treatment Group (N)	**Median (Months) [95% CI]**	**Hazard Ratio [95% CI]**	**P-value (Log-Rank Test)**
Overall Survival				
FAS (n = 731)	Erlotinib (488)	6.7 [5.5 to 7.8]	0.76 [0.64 to 0.91]	0.0018
	Placebo (243)	4.7 [4.1 to 6.3]		
WT EGFR (n = 150)	Erlotinib (102)	8.1 [5.8 to 10.9]	0.75 [0.52 to 1.10]	0.1443

	Placebo (48)	3.4 [2.5 to 6.8]		
Progression-Free Survival				
FAS (n = 731)	Erlotinib (488)	2.2 [1.9 to 2.9]	0.64 [0.54 to 0.75]	< 0.0001
	Placebo (243)	1.8 [1.8 to 1.9]		
WT EGFR (n = 150)	Erlotinib (102)	2.2 [2.0 to 4.0]	0.56 [0.39 to 0.81]	0.0013
	Placebo (48)	1.8 [1.6 to 1.9]		
Response Rates				
		Response Rate (CR + PR) [95% CI]	**Difference in Response Rate [95% CI]**	**P-value (CMH Test)**
FAS (n = 731)	Erlotinib (488)	39/488 (8.0%) [5.7 to 10.8]	7.17 [4.3 to 10.0]	<0.0001
	Placebo (243)	2/243 (0.8%) [0.1 to 2.9]		
WT EGFR (n = 150)	Erlotinib (102)	6/102 (5.9%) [2.2 to 12.4]	3.80 [-3.4 to 11.0]	0.3051
	Placebo (48)	1/48 (2.1%) [0.1 to 11.1]		

CMH: Cochran-Mantel-Haenszel; CI: confidence interval; CR: complete response; FAS: full analysis set; PR: partial response; SD: stable disease; WT EGFR: wild-type epidermal growth factor receptor.
Hazard ratio <1 is in favor of erlotinib. Cut-off date: 30 Jan 2004
[†]Best overall response of confirmed CR or PR; nonresponder is SD, disease progression, or missing.
[‡]95% CI for one sample binomial using Pearson-Clopper method.
*Approximate 95% CI for difference of two rates using Hauck-Anderson method.
Source: Module 2.7.3 Table 3

To further evaluate the efficacy of erlotinib in the context of EGFR WT patients, the MAH conducted two exploratory analyses of PFS and OS in clinically selected populations of patients considered to be a surrogate for WT EGFR population. The first was a pre-specified subgroup analyses based on squamous cell histology determined at randomization and baseline in Study BR.21. The incidence of EGFR mutations in patients with squamous cell carcinoma has been reported to be low enough that the National Clinical Cancer Network (NCCN) does not recommend routine EGFR testing in this population unless they have never smoked, if only a small biopsy specimen (i.e. not a surgical resection) was used to assess histology, or if the histology is mixed [NCCN Guidelines, 2017]. Consequently, NSCLC patients with squamous cell histology subtype can be considered a clinically selected surrogate for the NSCLC EGFR WT population.

Results of this subgroup analysis showed that among patients with squamous cell histology (144 erlotinib; 78 placebo), the median survival of patients who received erlotinib (5.57 months; 95% CI 4.67, 7.00) was longer than in the placebo group (3.58 months; 95% CI 3.15, 4.34) with non-overlapping confidence intervals. The HR of 0.67 (95% CI 0.50, 0.90) was similar to that observed in both the ITT analysis for OS reported overall in Study BR.21 (HR = 0.76; 95% CI 0.64, 0.91) and the retrospective exploratory subgroup analysis of OS in WT EGFR patients. Similarly, median PFS for squamous cell patients receiving erlotinib was 9.86 weeks (95% CI 8.57, 15.14) compared with 7.86 weeks (95% CI 7.43, 8.14) for placebo patients. The HR of 0.53 (95% CI 0.39, 0.70) was consistent

both with the value observed in the overall ITT analysis for PFS (HR = 0.64; 95% CI 0.54, 0.75) and with the retrospective exploratory subgroup analysis of PFS in WT EGFR patients.

The second analysis was a retrospective analysis of the subgroup of male, smoker (or ex-smoker) patients with squamous NSCLC from the BR.21 study. In this subgroup, the incidence of EGFR-activating mutations is expected to be even less frequent than in the overall squamous NSCLC population because EGFR mutations are known to be more frequent among patients with female gender, who have never smoked, and with non-squamous histology subtype [Paz-Ares et al. 2010]. This population thus serves as a clinical surrogate for the WT EGFR population.

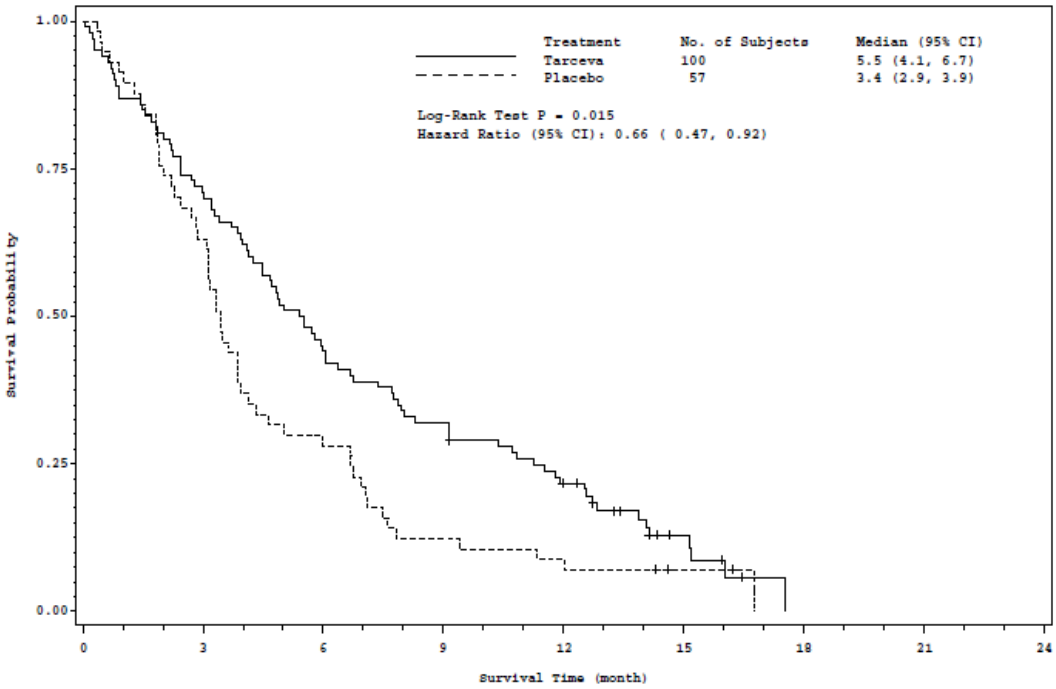
The subgroup analysis of male, current and former smokers diagnosed with squamous histology (n=157) demonstrated a survival benefit in favor of erlotinib, which was consistent with the results for the FAS in Study BR.21: median survival times were 5.5 months (95% CI: 4.1, 6.7) in patients treated with erlotinib and 3.4 months (95% CI: 2.9, 3.9) in patients treated with placebo. The HR in favor of erlotinib was 0.66 (95% CI: 0.47, 0.92; exploratory p-value = 0.015) (Figure 18, upper panel). Similarly, median PFS was 2.4 months (95% CI: 2.0, 3.6) in patients treated with erlotinib and 1.8 months (95% CI: 1.6, 1.8) in patients treated with placebo with a HR in favor of erlotinib of 0.43 (95% CI: 0.30, 0.62; exploratory p-value < 0.001) (Figure 18, lower panel).

Since a higher than expected percentage of patients in both treatment groups whose tissue samples were retrospectively tested for EGFR-activating mutations showed a positive test result in this sample (3/29 [10.3%] in erlotinib patients; 5/21 [23.8%] in placebo patients), a further sensitivity analysis was conducted excluding the 8 patients who tested positive for EGFR mutations. Results for OS and PFS remained consistent with the overall OS and PFS analyses in male, squamous smoker patients (i.e. the WT EGFR surrogate population). Median OS was 5.4 months (95% CI: 4.1, 6.4) in patients treated with erlotinib and 3.4 months (95% CI: 2.7, 3.9) in patients treated with placebo, with an HR in favor of erlotinib of 0.66 (95% CI: 0.46, 0.95; exploratory p-value : 0.022). Median PFS was 2.6 months (95% CI: 2.0, 3.6) in patients treated with erlotinib and 1.8 months (95% CI: 1.6, 1.8) in patients treated with placebo with an HR in favor of erlotinib of 0.44 (95% CI: 0.31, 0.64; exploratory p-value □ 0.001). Thus, even after excluding 8 patients from this subgroup with EGFR mutant positive NSCLC, these data still support the efficacy of erlotinib in WT EGFR patients.

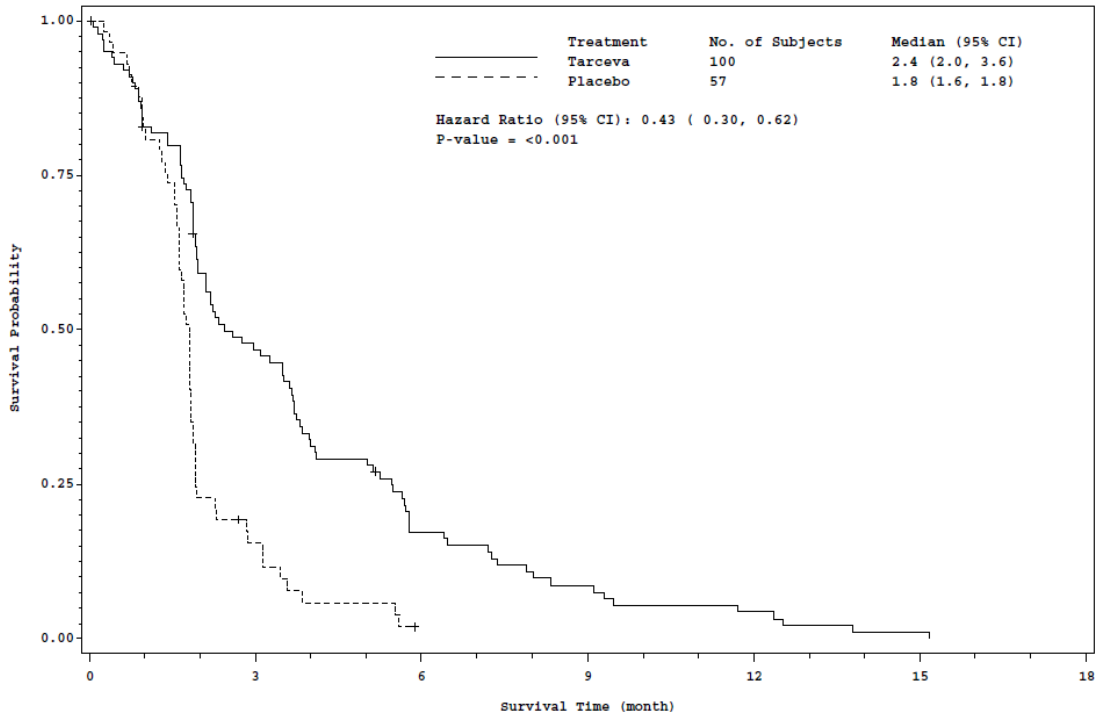
Taken together, the clinical data from the pivotal BR.21 study support the conclusion that erlotinib is efficacious in EGFR WT patients. While the magnitude of erlotinib activity is higher in EGFR-activating mutations, there is a clinically meaningful effect in EGFR WT patients who had failed at least one line of chemotherapy.

Figure 18 Kaplan-Meier curves of OS (upper panel) and PFS (lower panel) for the male, smoker subgroup of NSCLC patients with squamous cell histology (Study BR.21)

Overall Survival



Progression-Free Survival



Supportive clinical studies from the literature

Several published papers have shown erlotinib to have clinical responses similar to chemotherapy (pemetrexed and docetaxel) in NSCLC WT EGFR patients. The results of these studies are consistent in supporting the benefit of erlotinib in patients who have failed at least one line of chemotherapy across different patient populations as shown by the data from the pivotal study BR.21.

There are two published clinical studies that specifically enrolled NSCLC WT EGFR patients. The first study, by Li et al [2014], was an open-label, randomized Phase 2 study comparing erlotinib with pemetrexed in 123 patients with confirmed WT EGFR and EGFR fluorescence in-situ hybridization (FISH)-positive NSCLC who had progressed following standard platinum-based 1L chemotherapy. The results showed no significant differences for the efficacy between erlotinib and pemetrexed. Median PFS was 4.1 months (95% CI: 1.6, 6.6) on erlotinib and 3.9 months (95% CI: 2.7, 5.1) on pemetrexed and the difference was not statistically significant (HR = 0.92; 95% CI: 0.62, 1.37; p = 0.683). Response rates were higher among erlotinib-treated patients compared with those receiving pemetrexed (19.7% vs 8.1%). There was no significant difference in OS between the pemetrexed and erlotinib treatment groups (HR = 1.01; 95% CI: 0.66, 1.54). The findings with erlotinib in this study are consistent with the results of Study BR.21.

The second study (TAILOR) was a multicenter, controlled open-label study which prospectively evaluated erlotinib versus docetaxel as 2L treatment in 122 patients with confirmed WT EGFR NSCLC who had progressed following standard platinum-based chemotherapy; treatment crossover after further disease progression was not permitted [Garassino et al. 2013]. The primary analysis of OS reported the unadjusted HR of docetaxel to erlotinib to be 0.78 (95% CI: 0.51, 1.05; p = 0.1) and the adjusted HR to be 0.73 (95% CI: 0.53, 1.00; p = 0.05). PFS was shown to be significantly longer with docetaxel than with erlotinib with an adjusted HR = 0.71 (95% CI: 0.53, 0.95; p = 0.02) while the median PFS data were similar (2.9 months for docetaxel and 2.4 months for erlotinib).

While the TAILOR study demonstrated a favorable outcome for docetaxel over erlotinib in this treatment setting, there are a number of issues with the study design and analyses which suggest that the results should be interpreted with caution [Moro-Sibilot et al. 2014; Dafni et al. 2014]. These include the modification of the study design after 4 out of 5 years of patient recruitment at which time the blinded interim OS results were known, as well as the lack of Type I error adjustment of the interim analysis which led to the study design change. The study excluded patients who had prior exposure to taxanes, therefore the study population may not have been truly representative of a 2L patient population, and there were potentially important imbalances in histology and smoking status between the two treatment arms. With regards to analysis of the study endpoints, scans were not independently reviewed, introducing the potential for bias in the interpretation of the PFS results, the adjusted HR for OS was not adjusted based on predefined stratification factors, and there was no adjustment of the threshold for statistical significance for the multiple tests performed on the OS difference.

Notwithstanding the concerns surrounding the TAILOR study design and analysis, the difference in OS only just met the criteria for statistical significance in the adjusted analysis, while no statistically significant difference in OS was observed in favor of either treatment in the study by Li et al. [2014]. Taking into account the conflicting results with regards to PFS reported in these two studies and the favorable safety profile of erlotinib versus docetaxel or pemetrexed chemotherapy, erlotinib and chemotherapy can both be considered valid treatment options for WT EGFR NSCLC patients after failure of at least one chemotherapy regimen.

There are 4 published clinical studies in which subgroup analyses were made based on EGFR mutational status determined in a subset of the patients enrolled.

The PROSE study randomized patients to erlotinib or docetaxel/pemetrexed and EGFR status was determined in 177 patients, of whom 163 were WT EGFR [Gregorc et al. 2014]. Median PFS was shorter in the erlotinib arm, but median OS was 9.0 months in the erlotinib arm compared to 9.3 months in the chemotherapy arm which was not statistically significant (HR = 1.05; 95% CI: 0.75, 1.47; p = 0.757). This study showed that erlotinib has a similar effect on OS as chemotherapy in WT EGFR NSCLC patients in the 2L setting.

The DELTA study was a multicenter, open-label, randomized, Phase 3 study conducted in 41 centers across Japan evaluating the efficacy and safety of erlotinib versus docetaxel as second- or third line therapy in EGFR-unselected patients with advanced NSCLC whose disease had progressed following previous treatment with one or two chemotherapy regimens, including at least one platinum agent [Kawaguchi et al. 2014]. Of 255 patients in whom EGFR mutational status was determined, a total of 199 patients were confirmed with WT EGFR tumors. In the WT EGFR group, median PFS was 1.3 months with erlotinib compared with 2.9 months with docetaxel (HR = 1.45; 95% CI: 1.09, 1.94; p = 0.01). A supportive Cox analysis with stratification factors confirmed the significant difference (adjusted HR = 1.57; 95% CI: 1.18, 2.11; p < 0.01). However, there was no difference in OS between the erlotinib and docetaxel treatment arms (HR = 0.98; p = 0.91). The median OS was 9.0 months (95% CI: 7.8, 14.5) in the erlotinib group and 10.1 months (95% CI: 7.3, 12.4) in the docetaxel group (95% CI: 0.69, 1.39). Thus, while this study in an EGFR-unselected population showed a small treatment benefit with respect to PFS for patients treated with docetaxel, there was no difference between erlotinib and docetaxel with respect to OS.

The TITAN study was a multicenter, randomized, open-label Phase 3 study comparing erlotinib and chemotherapy as 2L treatment in NSCLC patients [Ciuleanu et al. 2012]. The study was halted prematurely due to slow recruitment after a median follow up of 27.9 months in the erlotinib arm and 24.8 months in the chemotherapy arm. As a result, the statistical plan was modified and the power of the statistical analyses to detect a difference in OS between treatments was reduced to 60%, hence, some of the analyses were underpowered to detect clinically meaningful treatment effects. Median OS was 5.3 months in the overall population, and there were no differences between the 2 treatment arms in terms of OS in the WT EGFR subpopulation, where the median OS was approximately 7 months. These results are consistent with the results of the BR.21 study.

The HORG study investigated the efficacy of erlotinib compared to pemetrexed in the 2L and 3L setting [Karampeazis et al. 2013]. There were 112 patients with confirmed WT EGFR status. There was no difference in terms of OS between the treatment arms (HR = 1.19; 95% CI: 0.77; 1.84); median OS in the erlotinib group was 9.7 months. Thus, pemetrexed and erlotinib showed comparable efficacy in this population of pre-treated patients with metastatic NSCLC.

Since the rate of EGFR mutations is very low in squamous cell histology [NCCN guidelines], this patient population may be considered as a clinically selected surrogate for the NSCLC EGFR WT population. Thus, the LUX-lung 8 study, which enrolled patients with squamous NSCLC, can be considered a clinically selected WT EGFR population and contributes to the overall picture consistently showing that erlotinib has an effect in WT EGFR patients. This study, which led to the approval of afatinib (an irreversible, pan-HER inhibitor) in squamous cell carcinoma, was a Phase 3, open-label, randomized study using erlotinib as a comparator in 795 patients with Stage IIIB/IV squamous cell carcinoma that had failed 1L therapy [Soria et al. 2015]. In this patient population (used as a clinical surrogate for

WT EGFR patients in Study BR.21), erlotinib had a median OS of 6.8 months, which was consistent with the effect seen in the squamous cell subgroup analyzed in Study BR.21.

To look more closely at the significance of the data from these studies as a whole, meta-analyses of pooled data from these clinical studies were performed and showed no statistically significant difference in OS between erlotinib and chemotherapy in patients with advanced NSCLC with WT EGFR. The first of these meta-analyses combined data from Phase 2 or Phase 3 prospective, randomized, controlled clinical studies where patients had histologically confirmed Stage IIIb or IV NSCLC with WT EGFR tumors or where a subgroup analysis for WT EGFR patients had been performed, the experimental group had received gefitinib or erlotinib, and the control group had received chemotherapy [Zhao 2014]. Based on these criteria, 6 studies were included with data from 990 patients with WT EGFR tumors. Among the 3 large studies comparing erlotinib to chemotherapy, there was no difference in OS between patients treated with erlotinib and those treated with chemotherapy (HR = 1.02; 95% CI: 0.83, 1.26, p = 0.84) (Table 3). There was also no significant difference in OS between any EGFR-TKI and chemotherapy groups across all 6 studies (HR = 1.02; 95% CI: 0.87, 1.20, p = 0.81)).

Table 2 Comparison of OS estimates for Erlotinib versus Chemotherapy in Meta-analyses of Second and Subsequent-Line Therapy in WT EGFR Patients (Zhao 2014)

Study	Analysis Set	Treatment	N	Median OS (months)	HR (95% CI)
TITAN [Ciuleanu et al, 2012]	Subset	Erlotinib	75	6.6	0.85 (0.59, 1.22)
		Doc/Pem	74	4.4	
TAILOR [Garassino et al, 2013]	All	Erlotinib	110	5.4	1.28 (0.89, 1.84))
		Doc	109	8.2	
DELTA [Kawaguchi et al, 2014]	Subset	Erlotinib	109	9.0	0.98 (0.69, 1.39)
		Doc	90	10.1	
Meta-analysis of the above 3 studies [Zhao et al, 2014]	Erlotinib vs. chemotherapy		567	NR	1.02 (0.83, 1.26)
Meta-analysis of 9 Phase 2/3 trials [Vale et al, 2015]	Erlotinib or gefitinib vs. chemotherapy		1400	NR	1.06 (0.93, 1.22)

NR: Not reported; OS: overall survival; Pem: Pemetrexed; Doc: Docetaxel; WT EGFR: wild-type epidermal growth factor

A second meta-analysis was based on a systematic review of studies of EGFR TKIs versus chemotherapy as 2L therapy after first-line chemotherapy in randomized patients with advanced NSCLC WT EGFR tumors and patients with tumors harboring EGFR mutations, irrespective of sex, age, histology, ethnicity, smoking history, or EGFR mutational status, and who had not received prior TKI treatment [Vale et al, 2015]. Based on these criteria, 9 studies were included with data from 1302 patients (including studies evaluated in the meta-analysis by Zhao et al [2014]). Results showed a PFS HR of 1.31 (95% CI: 1.16, 1.48; P < 0.0001) in favor of chemotherapy. There was no evidence in this meta-analysis of a difference between the effect of TKIs or chemotherapy on OS (HR = 1.06; 95% CI: 0.93, 1.22).

Thus, these meta-analyses show that both erlotinib and chemotherapy can be considered as valid treatment options with clinical benefit for WT EGFR NSCLC patients in the 2L and further line settings.

In summary, the pattern that emerges on looking across all of these clinical studies that either specifically enrolled WT EGFR patients or included subgroups of WT EGFR patients, is that there is no discernable difference in efficacy with erlotinib compared to chemotherapy with a favorable safety and tolerability profile for erlotinib in patients with WT EGFR in second or further lines of treatment.

Supportive case studies from the literature

There are two published case studies that demonstrate a positive response to erlotinib in the 2L setting in WT EGFR patients who did not have the clinical predictors of positive outcome as previously reported in the literature. These cases emphasize the importance of considering erlotinib as a treatment option for any patient in the 2L, 3L or maintenance setting.

The first was published in 2012 and reports on a 71-year-old white man with a 50 pack-year history of smoking who had stage IV NSCLC that was WT EGFR [Karam and Melosky 2012]. The patient initially had partial response (PR) after radiotherapy and 3 cycles of chemotherapy (first-line gemcitabine-cisplatin) but an additional node was identified 2 weeks after completion of the 4th cycle of chemotherapy. Erlotinib treatment was initiated as 2L therapy on 24 August 2010. After 18 days at 150 mg daily, treatment was stopped for 2 weeks due to a grade 3 rash, then reinitiated at 100 mg daily on 4 October 2010. By 26 October 2010, 2 of 3 lesions had decreased in size and the third was no longer measurable. The dose was increased again to 150 mg daily in January 2011 due to an improvement in the rash. Subsequent CT scans in February 2011 showed that the 3 lesions had achieved PR according to RECIST criteria. The patient was still on erlotinib treatment after 6 months and the authors anticipate that he would achieve a survival benefit because he had already exceeded the PFS of 2.2 months reached in the BR.21 study.

The second case was published in 2017 and reports on a 65-year-old white man who was a heavy smoker with WT EGFR squamous NSCLC [Gambale et al. 2017]. After surgical right pneumonectomy and ipsilateral hilar-mediastinal lymphadenectomy in October 2009, at which point a CT scan found no evidence of metastasis, the first post-surgery CT scan, in January 2010, revealed new nodules and spleen metastasis. The patient received first-line chemotherapy (4 cycles of carboplatin and gemcitabine) but continued to progress. Second-line, weekly docetaxel chemotherapy was stopped after the first cycle due to grade 4 neutropenia and atrial fibrillation. Due to the short disease progression-free interval and limiting bone marrow toxicity, further chemotherapy was ruled out. Erlotinib was started (150 mg/day) in March 2011, but was reduced to 100 mg/day after 1 month due

to grade 3 skin rash. The first post-treatment CT scan revealed stable disease (SD) according to RECIST criteria. The second CT scan, 4 months later, revealed continued SD with continued reduction of the paraesophageal lesion. Other than the skin toxicity, no other AEs were reported. CT scans performed every 4 months confirmed SD for 5 years after beginning erlotinib therapy, but due to the skin toxicity erlotinib treatment was then stopped in March 2016. Disease progression was documented 2 months after stopping erlotinib (May 2016).

CHMP assessment of the MAH's response

The IUNO study, which has been assessed in a previous variation, showed no benefit of early erlotinib treatment in patients with NSCLC without known EGFR activating mutations compared to placebo. In response to this IUNO study, the FDA decided to limit both the early switch-maintenance indication in and the second line indication.. In the EU, the IUNO study led to the revision of the maintenance indication and the benefit/risk balance in the second-line indication after failure of prior chemotherapy came into question, in particular for the patients without an EGFR mutation.

The MAH was asked to provide additional discussion on the clinical evidence in order to support activity of erlotinib (and therefore a positive benefit/risk balance of erlotinib) as second and beyond line of treatment of NSCLC patients with EGFR WT status. In the discussion the MAH was asked to include the concerns on the interpretability of the presented data, the patient population that is likely to benefit and the rational that EGFR signaling must the able to drive tumour growth in WT EGFR NSCLC.

1. Discuss the concerns on the presented data.

The subgroup analysis in WT EGFR patients of the BR.21 study is discussed in the initial application. However, the interpretability of the data is hampered by the post-hoc nature of the analyses. The applicant agrees that these data "could be challenged in view of the retrospective nature and the small sample size". However, the applicant indicates that the presented data in the answer consistently support the conclusion of a modest but clinically relevant benefit of erlotinib in patients with WT EGFR NSCLC. However, in the presented literature no clear distinction is made between EGFR and WT-EGFR. At the time that the presented literature was published, the activating mutation were not described yet and specific testing for these mutations was not yet common practice. Therefore, these publications do not provide the evidence specifically for WT-EGFR signalling, while needed for the purpose of this PAM

Furthermore, no additional/new information was provided in the discussion on the concerns raised for the subgroup analyses of the BR.21 study performed in NSCLC patients with EGFR WT status and/or with squamous histology. Therefore, the interpretability of the data on the efficacy of erlotinib compared to placebo is still hampered by the fact that analyses have been performed post-hoc and the possibility for false positives.

The other clinical data presented by literature studies do not provide enough evidence to overcome the concerns we have on the efficacy of erlotinib in the WT-EGFR NSCLC patients. The presented data still consist of a highly heterogeneous group of publications related to several studies performed in different populations, and/or in different treatment setting and/or employing different comparators. The interpretation of the results is hampered in several studies due to the limited sample size and the fact that EGFR WT patients represented only subgroups of the population treated in the study. Overall, conflicting results are presented in the literature, ranging from studies (e.g., TAILOR) clearly indicating superiority of chemotherapy vs erlotinib in terms of PFS and OS in EGFR WT patients and other trials/subgroup analyses suggesting no significant difference in OS when comparing chemotherapy to

erlotinib (for the TITAN, DELTA and PROSE trial). To be noted, a numerical trend in median PFS favouring chemotherapy was identified in all these trial.

In this round, the applicant proved new data by means of two case studies were presented. A 71-year-old white man with stage IV NSCLC that was WT-EGFR, which had PR of 3 lesions after erlotinib treatment (still on erlotinib after 6 months) and a 65-year-old white man with WT EGFR squamous NSCLC who had stable disease for 5 years after beginning erlotinib therapy (treatment stopped due to skin toxicity). Both case studies point towards an effect of erlotinib in these WT-EGFR patients. However, two case studies do not provide enough reliable evidence for erlotinib to be effective over chemotherapy in the general WT-EGFR NSCLC population.

In conclusion, the concerns on the interpretability of the clinical evidence to support erlotinib efficacy in WT-EGFR NSLCLC currently presented (by e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests) persist and therefore the extent of clinical benefit of erlotinib in second- and further-line WT EGFR NSCLC remains unclear.

2. Discuss the patient population that is likely to benefit

The applicant indicates that the patients population that benefits the most is the patients with EGFR-activating mutation, but that patients without these mutations may also benefit. Unfortunately the applicant did not discuss which specific patient population is likely to benefit among the patients with WT EGFR NSCLC. Due to the rapidly changing treatment landscape of NSCLC it is essential to pinpoint if, and if so, which patients with EGFR WT NSCLC truly benefit from the treatment with erlotinib.

It has been hypothesized that patients who failed chemotherapy and might therefore be chemotherapy-resistant exhibit higher EGFR-expression. As mentioned in the MAHs response to question 3 and 7, a differential response might exist in patients with low or high WT-EGFR expression. This conclusion is supported by the study by Li et al, in which only high EGFR expressing patients were included and comparable OS was seen when comparing erlotinib and chemotherapy (numerically) in favour of chemotherapy. It should be mentioned that, in the additional analysis performed by the MAH, the EGFR WT subgroup was defined as all patients excluding those subjects whose tumours had exon 19 deletions and exon 21 L858R mutations. Therefore patient with other indeterminate variants in EGFR were included (Zhu et al). Inclusion of the patients with indeterminate variants in EGFR hampers the interpretation of the results, as these patients might exhibit EGFR variants that do show constitutively active EGFR and therefore a rational for erlotinib efficacy. Although the data should be interpreted with caution, the analyses in response to question 7 (low vs high EGFR expression) suggest that patients expressing low amounts of WT-EGFR do not benefit from erlotinib treatment. This results in a negative B/R in these low expressing patients. The determination of EGFR-expression level is not common in clinical practice. Furthermore, no reliable standards and/or cut-offs exist to determine high and low EGFR expression in a consistent manner. Therefore, in clinical practice WT-EGFR NSCLC patients that possibly benefit from erlotinib treatment cannot be determined and the extent of the clinical benefit of erlotinib in the overall WT-EGFR population remains questionable.

3. The rational that EGFR signaling must the able to drive tumour growth in WT EGFR NSCLC.

The applicant was asked to provide both pre-clinical and clinical data to show that is WT EGFR signaling is able to drive tumour growth in patients with WT EGFR NSCLC.

It has been known for a long time that EGFR signaling is able to activate pathways related to tumor

growth. However, as discussed above, the pre-clinical data presented is based on EGFR research from an era before the existence of EGFR mutation was identified. Some of the referred pre-clinical studies make use of cancer cell lines. These cancer cell-lines might contain mutated instead of WT EGFR. Therefore, it is not clear whether the presented evidence may be 100% attributed to WT EGFR signaling specifically.

In addition, no (pre-) clinical evidence was presented to prove that this increased WT-EGFR expression result in increased activation of the WT EGFR signaling cascade and subsequently is able to be the driving force of tumour growth in patients with WT EGFR NSCLC.

Conclusion

The benefit/risk balance of erlotinib in the second-line and beyond treatment of patients with locally advanced or metastatic WT-EGFR NSCLC remains undetermined for the following reasons:
First, the concerns persist on the interpretability of the currently presented clinical evidence to support erlotinib efficacy in comparison to both placebo as chemotherapy in WT-EGFR NSLCLC (by e.g. limited samples size, post-hoc analyses, heterogeneity of the data, different mutational tests).
Second, it has been known for a long time that EGFR signalling is able to activate pathways related to tumour growth, however, based on the presented (pre-)clinical evidence it is unclear to what extent the activity can be attributed to WT EGFR signalling specifically.

Therefore, the Major Objection is NOT resolved and the benefit/risk balance cannot be established in the NSCLC patients with WT EGFR mutations.

During the procedure the MAH has proposed to reflect the uncertainties in relation to the 2nd-line and beyond NSCLC indication including the following wording in section 4.1 of the SmPC:

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated, when other treatment options are not considered suitable.

The CHMP agreed to this revision of the indication.

Point resolved.

Question 2

No clinical data are presented to justify the idea of erlotinib inhibiting the ILK-parvin-PINCH (IPP) complex and epithelial to mesenchymal transition (EMT). Could the MAH discuss the available clinical data to confirm the hypothesis of erlotinib inhibiting the IPP complex and subsequent EMT.

Summary of the MAH's response

The MAH is not suggesting that the hypothesis for the ability of erlotinib to inhibit the IPP complex or the EMT is the main mode of action of erlotinib, which is via direct and reversible inhibition of the EGFR tyrosine kinase, but simply that these other activities may also play a secondary role in erlotinib's

activity in WT EGFR [Zhang et al. 2009; Augustin et al. 2013]. There are no clinical data to support this hypothesis; these secondary pathways of activity were discussed as an exploration of reasons for why erlotinib exhibits activity in the WT EGFR tumors in clinical studies when gefitinib does not, as a component of the totality of our current knowledge.

One additional reason for the difference between the effect of erlotinib and gefitinib in WT EGFR NSCLC patients has been suggested to be the higher exposure/mg dose that is obtained with erlotinib compared with gefitinib. The therapeutic dose of erlotinib is 150 mg/day (max tolerated dose), which results in an AUC of 38.42 µg*h/mL, and is 7-fold higher than the exposure obtained at the gefitinib therapeutic dose (250 mg/day) [Bronte 2014]. For gefitinib to reach a comparable AUC of 36.08 µg*h/mL, an estimated dose of 700 mg/day would be required, which is 2.8-fold higher than the gefitinib therapeutic dose of 250 mg/day. Preclinical studies found that higher exposures of erlotinib were needed to inhibit the growth of EGFR WT tumors compared to EGFR mutant tumors [Siegel-Lakhai et al. 2005; Carey et al. 2006]. In addition, the major metabolite of erlotinib retains most of its EGFR inhibitory activity whereas the major metabolite of gefitinib is significantly less active, which may also contribute to the observed difference in clinical outcome [erlotinib Investigators Brochure; McKillop et al. 2006].

CHMP assessment of the MAH's response

It is acknowledged that the possible inhibition of the IPP complex may also play a secondary role in erlotinib's activity in WT EGFR. However, this idea and the idea regarding higher exposure of erlotinib compared to gefitinib remain suggestive rove.

As no clinical data on inhibition of the IPP complex by Erlotinib is available, no further action is required on this question.

Issue Resolved.

Question 3

The MAH suggest that the difference between chemo-sensitive and chemo-resistant tumors is mainly based on the EGFR expression, which is higher in resistant cells. This would, in view of the MAH, constitute the rationale supporting activity of erlotinib in EGFR WT NSCLC patients. However, the early switch maintenance therapy with erlotinib performed in the IUNO study, enrolling patients with high EGFR expressing levels, did not result in a better efficacy than with placebo. Therefore, "high" EGFR expression due to chemo-resistance cannot be the only reason for erlotinib showing a benefit in 2L- and further-line treatment in EGFR WT NSCLC. The MAH should comment on this observed discrepancy

Summary of the MAH's response

EGFR expression levels were not tested as part of the IUNO study and high EGFR expression levels were not an inclusion criterion for the IUNO study. The only enrollment criterion related to EGFR was exclusion of patients whose tumors harbored an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutations, either known at screening or confirmed by central testing before randomization).

The reason early switch maintenance therapy with erlotinib did not result in a better efficacy than with placebo in the IUNO study may be because the study was restricted to patients who had disease control or showed a response to treatment with their 1L chemotherapy (i.e. patients who were not chemotherapy resistant). Based on the preclinical findings from published literature WT EGFR patients

who have disease control or response to 1L therapy (i.e. those patients enrolled in the IUNO study) are not likely to benefit from treatment with a TKI.

Disease progression in patients treated with chemotherapy develops as tumor cells acquire chemotherapy resistance. Preclinical and clinical observations suggest that as tumors develop resistance to chemotherapy, they develop a greater dependence on EGFR activity, which is associated with increased expression of EGFR (see the response to Question 1). The upregulation of EGFR expression in response to chemotherapy resistance, and the associated increased EGFR activity, is linked to acquired sensitivity to EGFR TKI's. Preclinical data from parental tumor cell lines (chemosensitive) with chemotherapy drug-resistant variants of those cell lines showed that some tumor cells with initial low EGFR expression levels and thus sensitivity to erlotinib increased the expression of EGFR and developed greater sensitivity to erlotinib when they became resistant to chemotherapy [Dai et al. 2005]. Similar increased expression and greater EGFR TKI sensitivity by drug resistant tumor cells has been observed in breast cancer cells that have become resistant to tamoxifen [Britton 2006; Knowlden 2003; Massarweh 2008; Nicholson 2001; Osborne 2011]. Hence, patients treated in 1L maintenance who have not progressed on chemotherapy (IUNO population) may not derive any benefit from the addition of a TKI after completion of 4 cycles of chemotherapy whereas patients who have failed at least one course of chemotherapy and are chemotherapy resistant (BR.21 population), develop additional EGFR expression and activity that may positively influence response to treatment with a TKI.

As a result, patients treated with erlotinib after failure of at least one chemotherapy and progression of disease (i.e. chemotherapy-resistant patients and those enrolled in the BR.21 study) may respond to erlotinib due to a higher expression and activity of EGFR. This is consistent with the improved response to erlotinib compared to placebo that was seen in the BR.21 study.

This is also supported by the observation in the IUNO study that there was no discernable difference in survival when comparing patients treated with 2L erlotinib and 2L chemotherapy. If erlotinib had no efficacy at all in the 2L setting, one would have expected some incremental difference in OS in those patients who received 2L chemotherapy compared to 2L erlotinib, but this was not evident. Although the 2L portion of the study was not randomized nor designed or powered for a 2L efficacy analysis, the lack of a discernable difference between erlotinib and chemotherapy in the 2L phase of the IUNO study is consistent with the published data presented in the response to Question 1 (Clinical evidence) supporting comparability of erlotinib and chemotherapy in 2L. It is also consistent with the outcome of the OS analysis requested in Question 4, which suggest that patients benefited to a similar extent whether taking erlotinib or chemotherapy in 2L (see the response to Question 4).

Thus, the findings of the IUNO study in patients who were responding to their chemotherapy, and the findings of the BR.21 study in patients whose disease progressed on chemotherapy, are consistent with the proposed difference between chemo-sensitive and chemo-resistant tumors being based in part on EGFR expression and increased EGFR activity in those tumors. Further analyses based on EGFR expression levels in Study BR.21 have been presented in the response to Question 8.

CHMP assessment of the MAH's response

In the Tarceva EPAR it is stated that in the IUNO study all eligible patients were to have known EGFR by immunohistochemistry (IHC) status. This was interpreted in a way that all patients had to have known/measurable EGFR expression addressed by IHC. As apparently these patients did not have to have high EGFR expression no discrepancy is observed.

Conclusion: **Issue resolved.**

Question 4

The MAH suggest that no big difference can be detected between the OS of the 2L erlotinib and the 2L chemotherapy in the IUNO study. This OS is calculated with the starting point at randomization. The MAH is requested to provide the PFS and OS with a starting point at first time progression of disease (PD) to see whether still no difference is found between chemotherapy and erlotinib treatment (PFS2 and OS2)

Summary of the MAH's response

As requested, the analysis of OS has been performed and is provided below. It was not possible to perform the analysis of PFS as requested, the reasons for which are discussed below.

OS2 ANALYSIS (IUNO STUDY)

For the OS2 analysis, 281 patients were randomized to the late erlotinib arm and could receive erlotinib in 2L and 264 patients to the early erlotinib arm and could receive chemotherapy in 2L. There was no relevant difference in OS2 between the two treatment arms (Table 3 and Figure 19). Median OS was similar for both arms: 6.24 months for late erlotinib and 6.51 months for early erlotinib (HR = 0.97, 95% CI 0.8, 1.18). Taken together, these analyses suggest that patients benefited to a similar extent whether taking erlotinib or chemotherapy in 2L.

Table 3 Time to event summary for overall survival with a starting point at first time disease progression (OS2; IUNO Study)

Parameters	Late Erlotinib (N = 281)	Early Erlotinib (N = 264)
Patients with events, n (%)	211 (75.1)	201 (76.1)
Time to event, Months		
Median [95% CI]	6.24 [4.86; 7.03]	6.51 [5.39; 7.89]
Stratified analysis		
Hazard ratio [95% CI] [a]	1.00 [0.79; 1.27]	
p-value [a]	0.9939	
Unstratified analysis		
Hazard ratio [95% CI] [a]	0.97 [0.80; 1.18]	
p-value [a]	0.7798	

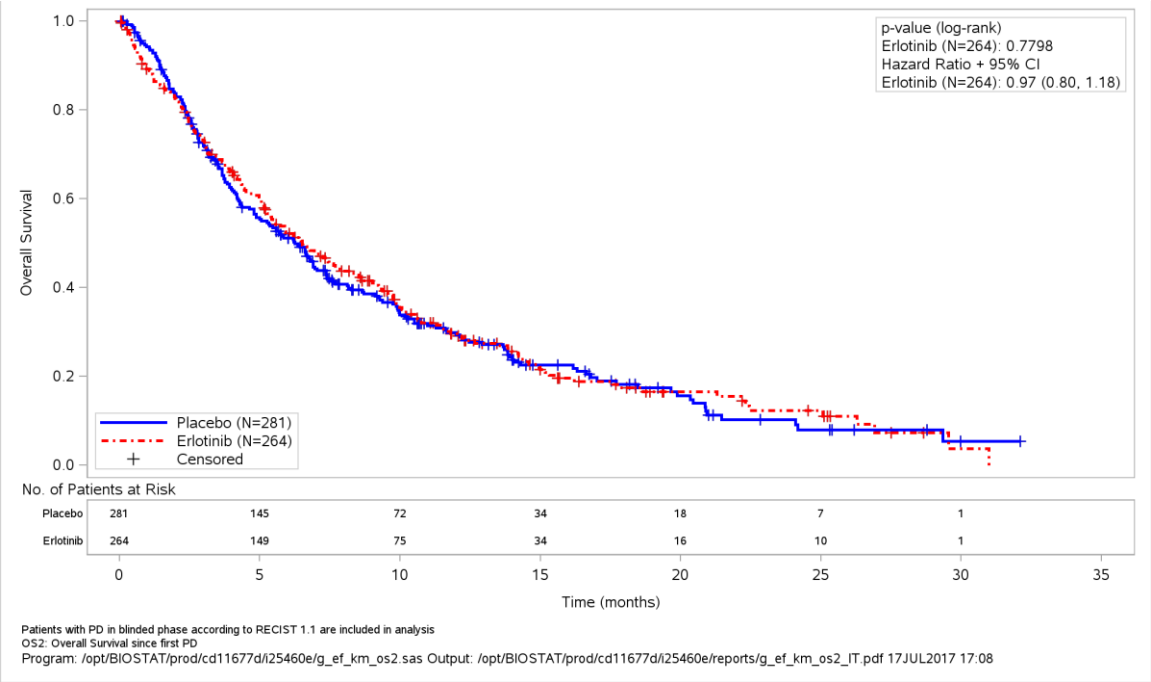
CI = confidence interval; N = number of patients included in the analysis.

OS2 = Overall Survival since first disease progression − Censoring: (1=censored, 0=event).

[a] 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.

Source: Appendix 1, Protocol BO25460, Table 1

Figure 19 Kaplan-Meier plot of overall survival since first disease progression (OS2; IUNO Study)



CI = confidence interval; ITT = intent to treat; OS2 = overall survival since first disease progression.

PFS2 ANALYSIS

According to the IUNO study protocol, after the patient had PD during the blinded phase, they could enter the open-label phase. However, patients in the open-label phase who had PD were managed according to local clinical practice (including drug administration, dose modification, tumor assessment schedule and methodology, and other factors). As a result, only 23 patients (5 randomized to the erlotinib arm and 18 to the placebo arm in the blinded phase) had tumor assessments after first time PD. Due to the limited and unbalanced number of patients with data, PFS2 analysis would not give meaningful results.

CHMP assessment of the MAH's response

The applicant provided the analysis as requested for OS2 and was not able to provide the data for PFS2 as tumour assessments were done routinely done at this point in the study. The applicant concludes that the OS analyses suggest that patient benefit to a similar extent when taking erlotinib or chemotherapy in 2L. Only OS2 data is available, which in this case is unfortunate as the patient were also treated 3L/4L with investigators choice. The exact contribution of these treatment cannot be determined without the PFS2 analysis.

Conclusion: No further action is required.

Issue Resolved

Question 5

In the BR.21 study only 233 of 328 samples were considered to be adequate for EGFR mutation analysis, of which in the end 204 could be tested for a EGFR mutation. The MAH is asked to elaborate on the criteria used to categorize a sample as adequate and to indicate

why for 29 samples no proper mutational analysis was obtained.

Summary of the MAH's response

The final study report for the BR.21 study was issued in 2004. Since activating-EGFR mutations were not identified as a predictive biomarker before 2004 [Lynch et al. 2004], the study had not planned analyses of EGFR mutational status. During the original study, 328 samples had been obtained for biomarker analysis according to the protocol (i.e. there was a biopsy sample for which the tissue was adequate for at least one biomarker analysis and for which informed consent had been obtained).

Post-hoc mutational analyses were subsequently performed. At the time of the post-hoc mutational analyses, the samples collected in the original study were assessed histologically by a pathologist. Over the course of the analyses, 233 (71% of the original set) samples were identified that were considered adequate, meaning they yielded sufficient DNA to amplify either all of exons 18 through 21 or just exons 19 and 21 alone [Tsao et al. 2005; Zhu et al. 2008]. The purified PCR products obtained from the DNA samples were sequenced in both directions and only sequence variations that were present in both directions in more than 15 percent of specimens were included in the analysis. As a result, of 233 samples with sufficient DNA for sequencing, mutational results were obtained for 204 patients [Zhu et al. 2008].

It is not unusual that not all samples collected during a study have adequate tissue to allow for mutational testing. In studies for which testing is done retrospectively, it is often problematic to get tissue samples from such a large proportion of the study population; tissue samples are often limited and may be subject to assay prioritization, which further reduces the samples available for the retrospectively planned tests. Thus, in the MAH experience, a sample size of 71% of the originally obtained samples is not unusual for a retrospective analysis and represents a large proportion of the available samples from Study BR.21.

CHMP assessment of the MAH's response

The applicant explained in more detail how the mutation analysis was performed and why some samples were considered inadequate for analysis, mostly related to amount and quality of DNA.

Issue Resolved

Question 6

In the BR.21 study the MAH should also present the EGFR expression level (as assessed by IHC) of patients with proper samples for mutational analysis.

Summary of the MAH's response

The requested data showing high (≥10%) and low (<10%) EGFR expression levels in patients with EGFR mutation status are provided in

Table 4. The EGFR WT subgroup was defined as all patients excluding those whose tumors had exon 19 deletions and exon 21 L858R mutations [Zhu et al. 2008]. Due to the small sample size in these subgroups, the results should be interpreted with caution.

Table 4 Summary of EGFR expression level in patients with proper samples for mutational analysis from Study BR.21

Phenotype	**EGFR-percent Cells Stained**			
	High (≥10%)	Low (<10%)	Unknown	Total

Erlotinib patients	N=61	N=51	N=18	N=130
Mutation	3 (4.9%)	7 (13.7%)	5 (27.8%)	15 (11.5%)
Wild Type	58 (95.1%)	44 (86.3%)	13 (72.2%)	115 (88.5%)
Placebo patients	N=35	N=27	N=12	N=74
Mutation	8 (22.9%)	5 (18.5%)	6 (50.0%)	19 (25.7%)
Wild Type	27 (77.1%)	22 (81.5%)	6 (50.0%)	55 (74.3%)

EGFR = epidermal growth factor receptor; N = number of patients included in the analysis.

Source: Appendix 1, Table 3

CHMP assessment of the MAH's response

The requested data is provided by the applicant. A slightly higher inclusion of patient with high EGFR expression can be seen.

Issue Resolved

Question 7

The MAH is asked to provide data on EGFR expression level of the samples in both the WT and squamous subgroup of the BR.21. Please provide the efficacy parameters (PFS and OS) for patients with low and high expression status in both the WT and squamous NSCLC subgroups.

Summary of the MAH's response

The requested subgroup analyses have been performed and are presented below.

Of the samples tested, 85 out of 170 (50%) of the WT EGFR patients had high expression and 66 out of 170 patients (39%) had low expression. The EGFR WT subgroup was defined as all patients excluding those whose tumors had exon 19 deletions and exon 21 L858R mutations [Zhu et al. 2008]. For the squamous NSCLC subgroup, 41 out of 222 patients (18.5%) had high EGFR expression and 26 out of 222 patients (11.7%) had low expression (Table 5).

Table 5 Expression status in WT EGFR and squamous NSCLC patient subgroups (Study BR.21)

Expression level	WT EGFR		Squamous	
	Erlotinib (N=115)	**Placebo (N=55)**	**Erlotinib (N=144)**	**Placebo (N=78)**
High (≥10%)	58 (50.4%)	27 (49.1%)	26 (18.1%)	15 (19.2%)
Low (<10%)	44 (38.3%)	22 (40.0%)	15 (10.4%)	11 (14.1%)
Unknown	13 (11.3%)	6 (10.9%)	103 (71.5%)	52 (66.7%)

WT EGFR = epidermal growth factor receptor wild type; N = number of patients included in the analysis; NSCLC = non-small cell lung cancer

Source: Appendix 1, Table 4

Post-hoc analyses were conducted to analyze PFS and OS for patients with high and low expression status (defined by the ≥10% vs <10% staining) in both the WT EGFR and squamous NSCLC subgroups in Study BR.21. Due to the small sample size in these subgroups, especially in the high and low expression subgroups in squamous patients, these results should be interpreted with caution.

WT EGFR SUBGROUP

In the WT EGFR subgroup, analyses suggest that the EGFR high expression group may derive more benefit from erlotinib than the EGFR low expression group. For PFS the median time to event was 9.57 weeks in the high expression group compared to 8.14 weeks in the low expression group, with an HR of 0.8 (95% CI: 0.57, 1.11) (Table 6). While there was little difference in PFS between erlotinib (median time to event 8.21 weeks) and placebo (median time to event 8.14 weeks) in low expression patients, in high expression patients PFS was considerably longer in the erlotinib patients (median time to event 17.43 weeks) compared to the placebo patients (median time to event 7.14 weeks), with a HR of 0.32 (95% CI: 0.19, 0.52) (Table 7 and Figure 20).

Table 6 PFS by EGFR expression in WT EGFR subgroup (Study BR.21)

	Low expression in WT EGFR patients (N=66)	**High expression in WT EGFR patients (N=85)**
Median time to event (weeks)	8.14	9.57
Hazard Ratio	0.8	
95% CI	(0.57; 1.11)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; PFS = progression-free survival; WT = wild type.

Source: Appendix 1, Table 5

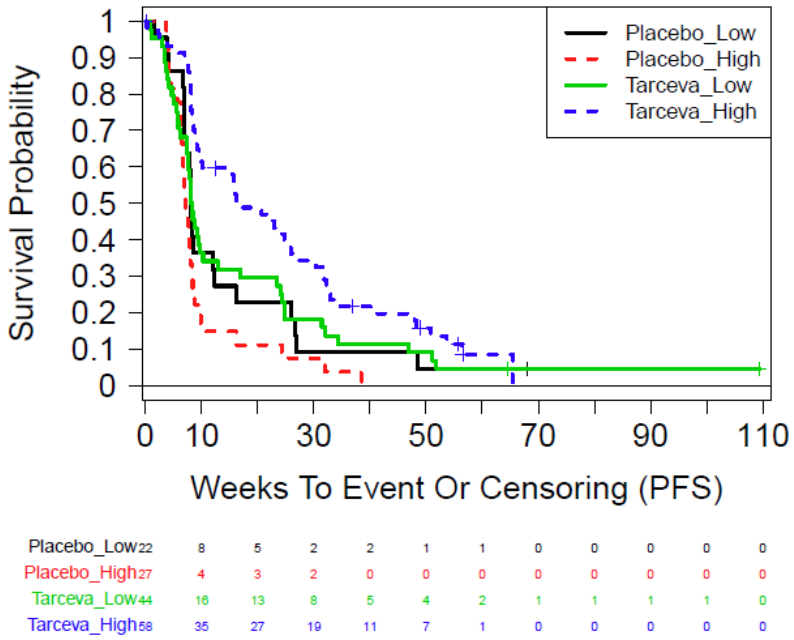
Table 7 PFS by EGFR expression and by treatment in WT EGFR subgroup (Study BR.21)

	Low expression in WT EGFR patients		High expression in WT EGFR patients	
	Placebo (N=22)	**Erlotinib (N=44)**	**Placebo (N=27)**	**Erlotinib (N=58)**
Median time to event (weeks)	8.14	8.21	7.14	17.43
Hazard Ratio	0.96		0.32	
95% CI	(0.57; 1.63)		(0.19; 0.52)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; PFS = progression-free survival; WT = wild type.

Source: Appendix 1, Table 6 and Table 7

Figure 20 Kaplan-Meier curve of PFS by EGFR expression (Study BR.21)



WT EGFR = epidermal growth factor receptor; PFS = progession-free survival.

The same outcome was seen for OS where the median time to event was 7.92 months in the high expression group compared to 6.28 months in the low expression group, with an HR of 0.81 (95% CI: 0.57, 1.16) (Table 8). The difference in OS between erlotinib (median time to event 5.9 months) and placebo (median time to event 7.04 months) was minimal in low expression patients, while in high expression patients OS was notably longer in the erlotinib patients (median time to event 11.53 months) compared to the placebo patients (median time to event 3.02 months), with an HR of 0.5 (95% CI: 0.3, 0.85) (Table 9 and Figure 21).

Table 8 OS by EGFR expression in WT EGFR subgroup (Study BR.21)

	Low expression in WT EGFR patients (N=66)	High expression in WT EGFR patients (N=85)
Median time to event (months)	6.28	7.92
Hazard Ratio	0.81	
95% CI	(0.57; 1.16)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; OS = overall survival; WT = wild type.

Source: Appendix 1, Table 11

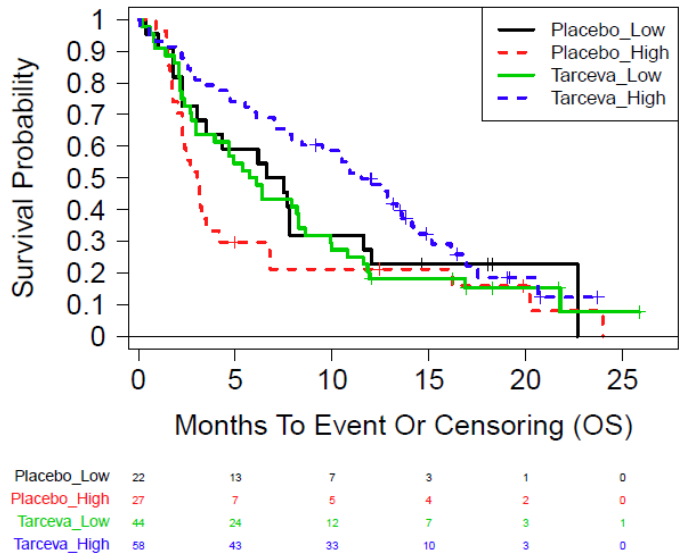
Table 9 OS by EGFR expression and by treatment in WT EGFR subgroup (Study BR.21)

	Low expression in WT EGFR patients		High expression in WT EGFR patients	
	Placebo (N=22)	Erlotinib (N=44)	Placebo (N=27)	Erlotinib (N=58)
Median time to event (months)	7.04	5.9	3.02	11.53
Hazard Ratio	1.12		0.5	
95% CI	(0.64; 1.96)		(0.3; 0.85)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; OS = overall survival; WT = wild type.

Source: Appendix 1, Table 12 and Table 13

Figure 21 Kaplan-Meier curve of OS by EGFR expression (Study BR.21)



WT EGFR = epidermal growth factor receptor wild type; OS = overall survival.

SQUAMOUS NSCLC SUBGROUP

A similar trend was seen in the squamous NSCLC subgroup. Although data are limited, they also suggest the EGFR high expression group may derive more benefit from erlotinib than the EGFR low expression group. The median time to event for PFS was 9.36 weeks in the high expression group compared to 7.79 weeks in the low expression group, with an HR of 0.72 (95% CI: 0.43, 1.2) (Table 10). While there was little difference in PFS between erlotinib (median time to event 8.00 weeks) and placebo (median time to event 7.43 weeks) in low expression patients, in high expression patients PFS was considerably longer in the erlotinib patients (median time to event 15.14 weeks) compared to the placebo patients (median time to event 8.29 weeks), with an HR of 0.39 (95% CI: 0.19, 0.79) (Table 11).

Table 10 PFS by EGFR expression in EGFR squamous subgroup (Study BR.21)

	Low expression in EGFR squamous patients (N=26)	**High expression in EGFR squamous patients (N=41)**
Median time to event (weeks)	7.79	9.36
Hazard Ratio	0.72	
95% CI	(0.43; 1.2)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; PFS = progression-free survival.

Source: Appendix 1, Table 8

Table 11 PFS by EGFR expression and by treatment in EGFR squamous subgroup (Study BR.21)

	Low expression in EGFR squamous patients		**High expression in EGFR squamous patients**	
	Placebo (N=11)	**Erlotinib (N=15**	**Placebo (N=15)**	**Erlotinib (N=26)**
Median time to event (weeks)	7.43	8.00	8.29	15.14
Hazard Ratio	1.08		0.39	
95% CI	(0.48; 2.42)		(0.19; 0.79)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; PFS = progression-free survival.

In the squamous subgroup, the median time to event for OS was 5.52 months in the high expression group compared to 4.67 months in the low expression group, with an HR of 0.8 (95% CI: 0.48, 1.33) (Table 12). As for PFS, in the high expression patients, OS was longer in the erlotinib patients (median time to event 7.66 months) compared to the placebo patients (median time to event 3.45 months), with an HR of 0.27 (95% CI: 0.12, 0.58) (Table 13). In the low expression groups, the

opposite was seen: OS was shorter in erlotinib patients (median time to event 4.14 months) than in placebo patients (median time to event 7.49 months). Owing to the very small sample size of these treatment arms, it is difficult to comment on the relevance of this difference.

Table 12 OS by EGFR expression in EGFR squamous subgroup (Study BR.21)

	Low expression in EGFR squamous patients (N=26)	**High expression in EGFR squamous patients (N=41)**
Median time to event (months)	4.67	5.52
Hazard Ratio	0.8	
95% CI	(0.48; 1.33)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; OS = overall survival.

Table 13 OS by EGFR expression and by treatment in EGFR squamous subgroup (Study BR.21)

	Low expression in EGFR squamous patients		**High expression in EGFR squamous patients**	
	Placebo (N=11)	**Erlotinib (N=15)**	**Placebo (N=15)**	**Erlotinib (N=26)**
Median time to event (months)	7.49	4.14	3.45	7.66
Hazard Ratio	2.72		0.27	
95% CI	(1.08; 6.86)		(0.12; 0.58)	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of patients included in the analysis; OS = overall survival.

CHMP assessment of the MAH's response

The requested analyses are performed and presented. It is acknowledged that the sample sizes of these requested analyses are low. Nevertheless they provide a hint toward the population with higher (WT)-EGFR expression, which seems have a benefit from erlotinib treatment.

It should be mentioned that the EGFR WT subgroup was defined as all patients excluding those whose tumours had exon 19 deletions and exon 21 L858R mutations. Therefore patient with other indeterminate variants in EGFR were included (Zhu et al). Inclusion of the patients with indeterminate variants in EGFR hampers the interpretation of the results, as these patients might exhibit EGFR variants that do show constitutively active EGFR and therefore a rational for erlotinib efficacy.

Issue Resolved

Question 8

The role of erlotinib might differ between maintenance and 2L treatment and this might be due to differential EGFR expression in chemotherapy-sensitive and a chemotherapy-resistant cells. The MAH is asked to perform subgroup analyses in the BR.21 study as a clinical argument for this hypothesis. Possible analysis that could be performed: Subgroup analysis (BR.21) on PFS and OS in patients who have a response or stable disease during the chemotherapy vs. patient progressing during chemotherapy.

Summary of the MAH's response

As noted in the response to Question 3, EGFR expression is not the main differentiator between chemo-sensitive and chemo-resistant tumour response to EGFR TKIs. The important difference is the change in usage of EGFR by the tumour as they adapt from chemo-sensitive to become chemo-resistant tumors, where increased expression of EGFR is one of the indicators of this adaptation.

Since all patients enrolled in the BR.21 study had disease which had progressed on chemotherapy (i.e. had chemotherapy-resistant disease), it was not possible to test a clinical hypothesis comparing patients who are sensitive to chemotherapy with patients who are resistant to chemotherapy.

However, in response to the request for a subgroup analysis to explore the role of erlotinib in WT EGFR maintenance and 2L treatment, subgroup analyses were made looking at differences in the best response to therapy prior to failing to respond to chemotherapy (Table 14). The response to erlotinib was compared between patients whose best response had been PD and thus had an immediate failure to respond to chemotherapy (i.e., an intrinsic resistance) and those patients whose best response was either SD or partial or complete response and thus only stopped responding to chemotherapy after having initially responded (i.e., an acquired resistance). Although the subgroup of patients with an immediate failure to respond to chemotherapy cannot be seen as a surrogate for patients who are sensitive to chemotherapy, the subgroup of patients who stopped responding to chemotherapy later on treatment can be seen as a surrogate for patients who have been on chemotherapy long enough to have acquired chemotherapy resistance and the associated increase in EGFR expression associated with this state.

This analysis was presented in the BR.21 study report as a subgroup analysis of best response to prior chemotherapy. It must be acknowledged that this analysis was an underpowered exploratory analysis, and no adjustments were made for the multiplicity of inferences in these subgroups. In addition, this comparison is clearly confounded by other factors such as the extent of disease upon initiation of treatment and how this relates to treatment failure.

Nonetheless, this analysis showed that patients who had a response or SD during prior chemotherapy (i.e. those that had acquired chemotherapy resistance) had a more beneficial response to treatment with erlotinib than those who had PD (i.e., had an immediate failure to respond to chemotherapy) (Table 14). This would be consistent with the idea that stopping to respond to chemotherapy after an initial response may be associated with more tumour evolution in terms of an increase in expression of EGFR.

Table 14 PFS by Best Response to Prior Therapy (Study BR.21)

Best Response to Prior Therapy	Erlotinib		Placebo			
	N	Median PFS Weeks (95% CI)	N	Median PFS Weeks (95% CI)	Hazard Ratio[a] (95% CI)	Log-Rank p-value
CR or PR	196	12.86 (8.57, 15.86)	96	8.14 (8.00, 8.57)	0.60 (0.46, 0.78)	<0.001
SD	191	11.00 (8.29, 16.14)	96	8.00 (7.57, 8.29)	0.66 (0.51, 0.85)	0.001
PD	101	8.14 (7.71, 9.29)	51	7.43 (6.57, 7.86)	0.64 (0.44, 0.91)	0.012

a. Erlotinib over placebo hazard ratio (Unstratified Log Rank Test)

CI = confidence interval; CR = complete response; N = number of patients included in the analysis; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Table 11-24 BR.21 CSR

CHMP assessment of the MAH's response

The MAH tried to provided data from the BR.21 study to provide evidence for the EGFR expression/chemoresistant hypothesis. Unfortunately the analysis is underpowered and confounded by other factors such as the extent of disease upon initiation of treatment and how this relates to treatment failure. Therefore, no conclusion can be drawn from the provided analysis.

Issue Resolved

7. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 09 November 2017