21 July 2011

EMA/657134/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tarceva

erlotinib

Procedure No.: EMEA/H/C/000618/II/0020

Note

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

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21 July 2011
EMA/CHMP/499608/2010
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/000618/II/0020

Invented name/name:	Tarceva
International non-proprietary name/common name:	erlotinib
Indication summary (as last approved):	treatment of non-small cell lung cancer and pancreatic cancer
Marketing authorisation holder:	Roche Registration Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication of Tarceva for the first-line treatment of locally advanced or metastatic NSCLC with activating EGFR mutations. The MAH also applied to revise the warnings on keratitis in section 4.4 of the SmPC and sections 2, 4 of the Package Leaflet following a request from the CHMP to harmonise the wording across EGFR inhibitor products. Annex II has also been updated to reflect the latest Risk Management Plan version number (RMP v. 3.1). The MAH took the opportunity to introduce amendments to the list of local representatives in the Package Leaflet.
Rapporteur: Co-Rapporteur:	Jens Ersbøll Pieter de Graeff
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2, 4 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	17 June 2010
Start of procedure:	27 June 2010
Rapporteur's assessment report circulated on:	27 August 2010
Co-Rapporteur's assessment report circulated on:	3 September 2010
Request for supplementary information and extension of timetable adopted by the CHMP on :	23 September 2010
MAH's responses submitted to the CHMP on :	18 November 2010
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	3 January 2011
2nd Request for supplementary information and extension of timetable adopted by the CHMP on :	20 January 2011
MAH's responses submitted to the CHMP on :	25 May 2011
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	4 July 2011
MAH's responses submitted to the CHMP on:	8 July 2011
Rapporteur's and Co-Rapporteur's updated joint assessment report circulated on:	14 July 2011
CHMP opinion:	21 July 2011

3. Scientific discussion

3.1. Introduction

Epidermal Growth Factor Receptors (EGFRs) are over-expressed in a number of tumours, including NSCLC. Erlotinib is an orally administered tyrosine kinase inhibitor (TKI). It is a small molecule specifically targeting the tyrosine kinase domain of the EGFR receptor which plays an important role in major signalling cellular pathways involved in tumour genesis and tumour growth.

Erlotinib (Tarceva) has already been approved for 2nd and further line treatment of patients with advanced (stage IIIB/IV) NSCLC and for maintenance therapy (in patients with SD) after 4 cycles of 1st line chemotherapy). Tarceva is also approved in the treatment of pancreatic cancer.

This application is for an extension of the NSCLC indication to add: *first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations".*

The indication is based on the results from study ML 20650 (EURTAC), an ongoing Phase III, open-label trial designed to evaluate the efficacy and safety of erlotinib treatment in previously untreated patients with advanced NSCLC who present mutations in the tyrosine kinase domain of EGFR as well as two bibliographic references were also presented as supportive:

- A prospective study conducted by the Spanish Lung Cancer Group (SLCG) (Rosell et al., N Engl J Med (2009), 361:958-67) which screened for EGFR mutations in patients with advanced NSCLC and treated eligible patients with erlotinib .
- A pooled analysis conducted by Paz-Ares et al. (Paz-Ares et al., J. Cell. Moll. Med. Vol 14, N01-2, 2010 pp.51-69) comparing the efficacy of first-line chemotherapy and EGFR TKIs (erlotinib and gefitinib) in patients with EGFR mutated tumours .

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (EMEA-000195-PIP0-08) for the following conditions:

- Non small cell lung cancer and pancreatic cancer

On the granting of a class waiver.

General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.2. Toxico-pharmacological aspects

The non-clinical information provided were extracted from scientific articles and mainly concern mutated forms of the EGFR, which have been found expressed in non-small cell lung cancer (NSCLC) tumor tissue in humans, and the differences between the mutated forms and the wild-type EGFR, and on the inhibitory potency of erlotinib on these forms of EGFR.

3. 2. 1. Pharmacology

3. 2. 1. 1. Primary pharmacodynamics

In vitro studies

The EGFR consists of an extra cellular ligand-binding domain, a transmembrane region, an intracellular kinase domain, and the C-terminal tail. The tail contains several tyrosine residues which can be phosphorylated.

On the cell surface, EGFR exists in a state of equilibrium between monomeric and dimeric forms: the binding partner is either another EGFR (homodimerization) or one of the other family members (heterodimerization). This equilibrium is shifted to the dimeric form in the presence of ligands, e.g. EGF. These ligands bind to the extracellular domain and stabilize the dimer (Lemmon, MA 2009**)**.

The kinase domain of EGFR consists of two lobes, one at the C-terminal (C-lobe), and the other at the N-terminal (N-lobe) with the active site in between the lobes. The kinase domain exists in two conformations, an inactive conformation, where the active site is 'closed' for substrates and the active conformation where the active site is 'open' for substrates.

In the active conformation of the kinase domain, the C-terminal tail bridges to the active site of the kinase domain and a phosphate group is transferred from ATP to one of several tyrosines of the C-

terminal tail. This catalytic cycle repeats itself (ADP leaves the active site, a new molecule of ATP enters, and again one phosphate group is transferred to another tyrosine on the tail). These phosphorylated motifs then recruit various adaptor molecules and thus a variety of signal pathways are activated which eventually leads to cell proliferation and survival (Bose R and Zhang X, 2009).

Erlotinib competes with ATP in its binding pocket, and thus eliminates the phosphorylation step and in this way hinders cell proliferation.

An enzymatic study (Qui C et al., 2009) of the nearly full-length wild-type EGFR protein in active (EGF-bound) and inactive (cetuximab inactivated) forms demonstrates that erlotinib binds to the activated form of the kinase domain of wild-type EGFR about ten-fold more tightly than to the inactive conformation. In this way it can efficiently block initiation of the signaling cascade (Table 1).

Table 1 Affinity of Erlotinib to Nearly-Full Length EGFR

EGFR	IC_{50} erlotinib (µM)
Wild-Type (EGF) [a]	0.486 ± 0.089
Wild-Type (cetuximab) [b]	4.4 ± 2.1

[a] wild-type EGFR in the presence of the ligand EGF: the kinase domain is in the active state
[b] wild-type EGFR with bound cetuximab: the kinase domain is in the inactive state

Several experiments indicate that in mutated EGFRs, the kinase domain is preferentially in the active conformation (Eck MJ and Yun CH, 2010).

Another major consequence of the activating mutations is that EGFR becomes functional in the absence of ligands. This was shown in cellular experiments which followed the phosphorylation of EGFR and the downstream signaling: In cells containing wild-type EGFR no phosphorylation and downstream-signaling is observed in the absence of EGF. In cells which contain EGFR (L858R) or EGFR(del), phosphorylation and signaling occurs constitutively, i.e. in the absence of EGF (Okabe T et al., 2007)

Since these mutations occur in the vicinity of the kinase domain, they influence the binding constants of ATP and erlotinib, and thus the ability of erlotinib to abrogate the signaling cascade and the cell proliferation. Structurally the EGFRs bearing activating mutations resemble the ligand-activated form of wild-type EGFR. Hence it may be expected that similarly the activating mutations may bind erlotinib and ATP better than wild-type EGFR. However, studies by Carey et al. using the isolated cytoplasmic kinase domain of mutated EGFRs, found that the picture is more complicated (Table 2).

Surprisingly, kinetic studies using the isolated cytoplasmic kinase domain of mutated EGFRs, found that while ATP binds less tightly to the mutated EGFRs, erlotinib binds tighter (Table 2). The ratio Ki[erlotinib] / Km[ATP] provides a relative estimate of the inhibitory potency. Thus it is estimated that erlotinib can inhibit the most common mutated forms of EGFRs approximately 10 – 100 fold more efficiently than the wild-type form (Carey et al).

Table 2 Affinities of erlotinib and ATP to wild-type and mutated EGFRs]

EGFR	Km[ATP] (µM)	Ki erlotinib (µM)	Ki[erlotinib] / Km[ATP] ($x10^{-3}$)
WT	5.0	0.0175	3.5
L858R	10.9	0.00625	0.57
Del(746-750)	129	0.003	0.025

The sensitivity of a comprehensive panel of EGFR mutations toward erlotinib was measured using Ba/F3 cells expressing the activating EGFR mutants (Kancha RK et al, 2009). The mutants caused IL-3 – independent growth in the Ba/F3 cells, indicating that these mutations lead to a growth advantage in vitro. The most abundant mutations are also the most sensitive ones (table 3).

Table 3 Inhibition of EGFR Mutants by Erlotinib.

EGFR	IC_{50} erlotinib (µM)
L858R	0.006
Del747-753insS	0.005
G719S	0.016
V742A	0.021
D761N	0.075
S768I	0.250
R776C	0.047
S784F	0.095
T790M	>2
G810S	0.057
N826S	0.505
L838V	0.160
L861Q	0.103
A864T	0.049

In vivo studies

The potential of these activating mutations to cause lung cancer was shown in transgenic mouse models (Politi K et al., 2006). These transgenic mice with doxycycline dependant expression of an exon 19 deletion mutant (EGFR (del L747–S752)) or the L858R mutant (EGFR (L858R)) in type II pneumocytes developed lung tumours within two weeks after induction with doxycycline. The mice expressing the EGFR (L858R) allele showed diffuse lung cancer highly reminiscent of human bronchioloalveolar carcinoma and later developed interspersed multifocal adenocarcinomas. In contrast, mice expressing EGFR (del L747–S752) developed multifocal tumors embedded in normal lung parenchyma with a longer latency. With mice carrying either EGFR allele, withdrawal of doxycycline (de-induction of the oncogene expression) caused rapid tumor regression.

Tumor bearing transgenic mice expressing the exon 19 deletion mutant (EGFR(del747–S752)) or the L858R mutant (EGFR(L858R)) in type II pneumocytes under the control of doxycycline were treated with erlotinib at doses of 12.5 mg/kg/day. Partial to complete responses evaluated by magnetic resonance imaging (MRI) was observed as early as 2 days after erlotinib treatment. The amount of tumor regression as assayed histologically correlated with the length of treatment. After 2-4 days of study treatment tumor cells were still observed throughout the lung sections. Very few tumor cells were detected in lung tissue from animals treated with erlotinib for > 2 weeks. Emphysematous changes and scarring were observed in the lungs of treated mice, presumably in areas where adenocarcinomas were eliminated or were being eliminated. Tumours in two mice that were heterozygous for p53, generated in the context of ongoing experiments to determine the effect of tumour suppressor gene deficiencies on mutant EGFR-dependent tumorigenesis, also regressed upon erlotinib treatment

These results suggest that inhibition of the kinase activity of the mutant receptor is sufficient to elicit responses similar to those observed upon de-induction of the EGFR oncogene in transgenic mice and to that observed after TKI treatment of most human lung tumors with EGFR mutations. In addition, in mice, both bronchioloalveolar carcinoma and solid invasive adenocarcinomas respond to treatment with erlotinib.

3. 2. 1. 2. Pharmacokinetic studies

No studies submitted.

3. 2. 1. 3. Toxicology

No studies submitted.

3. 2. 1. 4. Ecotoxicity/environmental risk assessment

See discussion on non-clinical aspects.

Discussion on non-clinical aspects

The MAH provided bibliographic data to support the efficacy of erlotinib for the treatment of human lung tumours with EGFR mutations.

The provided pharmacology data showed that erlotinib has higher affinity and efficacy at the active domain of the mutated EGFR than the wild-type receptor. In-vivo studies in tumour bearing transgenic mutant receptor mice treated with erlotinib showed and rapid regression of malignant lung tumours comparable to the effect observed in human lung tumours with EGFR mutations.

The estimated future environmental exposure in terms of surface water PEC to erlotinib even assuming a doubling of the use of erlotinib will be around 100 times lower than estimated in the first ERA and similarly for the other dependent PEC values and the risk ratios including the one for sediment. Therefore, the justification for not submitting a new ERA in the current application is deemed acceptable

Conclusion

The available literature describes the higher affinity and efficacy of erlotinib at the active domain of the mutated EGFR than the wild-type receptor. No additional non-clinical studies are considered necessary.

3.3. Clinical aspects

NSCLC accounts for approximately 85% of all cases of lung cancer. Although there has been a gradual decrease in the incidence of NSCLC in men, it continues to increase in women. The treatment of NSCLC is determined by disease stage. Surgery continues to be the mainstay of treatment for early-stage and localized disease. Over 70% patients with NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion. Current therapeutic options for advanced stage patients have the potential to palliate symptoms and extend survival; however, the disease is incurable. The median survival with support treatment alone (without chemotherapy) is approximately 3-4 months.

Platinum-based chemotherapy, when given as first-line therapy, modestly prolongs survival compared with best supportive care. Several third- generation chemotherapeutic agents (paclitaxel, pemetrexed, gemcitabine, docetaxel, vinorelbine and irinotecan) have also shown single-agent activity. In randomized Phase III trials, these agents in combinations with platinum have been associated with improved quality of life (QoL) and modest improvements in survival. However, no doublet regimen has proved superior and survival outcomes are poor (median survival, 8-10 months; 1 year survival rate 35% to 40%). Furthermore, platinum-based chemotherapy is associated with several life-threatening short-term side effects (e.g. febrile neutropenia and sepsis) as well as long-term side effects. This is particularly relevant for the use of cisplatin which can cause neuropathy that may be exacerbated when combined with other potentially neurotoxic agents such as paclitaxel or vinorelbine. Additionally,

there is a sub-set of patients from whom cisplatin-based doublets are not indicated as they have poor performance status and are at risk of life-threatening toxicities.

Advances in the knowledge of tumour biology and mechanisms of oncogenesis have granted the singling out of molecular targets for NSCLC treatment. Bevacizumab, a vascular endothelial growth factor (VEGF) monoclonal antibody, has been approved in many countries (including the EU) for use in combination with platinum-based chemotherapy in the first-line treatment of patients with unresectable advanced or metastatic non-squamous NSCLC on the basis of two phase III randomized trials. These represent the first evidence of improvement in treatment outcomes of chemotherapy with targeted therapies in the first-line treatment of advanced NSCLC.

Epidermal Growth Factor Receptors (EGFRs) are over-expressed in a number of tumours, including NSCLC. The tyrosine kinase domain of the EGFR receptor plays an important role in major signalling cellular pathways involved in tumour genesis and tumour growth.

Erlotinib is an orally administered tyrosine kinase inhibitor. It binds to the intracellular kinase domain of the EGFR in competition with ATP. In patients with mutations in the kinase domain, the binding constants for ATP and erlotinib are altered leading to more tightly binding of erlotinib. In result, erlotinib blocks mutated EGFR more efficiently. Furthermore, it has been demonstrated that tumours with activating EGFR mutations are more dependent on EGFR signalling for their proliferation. In consequence, activating mutations in the EGFR gene confer hypersensitivity to TKIs and increased responsiveness to TKIs why these mutations are strong, positive predictors of response to this kind of therapy. Studies have shown that mutations in certain *exons* of the EGFR gene have been consistently correlated with increased efficacy in response to EGFR TKIs.

Activating EGFR mutations are most frequently identified in Asians, in adenocarcinomas, in women and in non-smokers. The most frequently observed mutations are represented by single-point mutations in *exon 21* and deletions in *exon 19*. The number of patients with activating mutations is relatively limited in Europe: The reported prevalence of these activation mutations is about 10-15% in Caucasian populations compared to 30% in Asian populations.

Erlotinib is approved for the treatment of stage IIIB/IV NSCLC in the maintenance (in patients with stable disease (SD) after 4 cycles of 1st line chemotherapy), 2nd and further-line setting.

In the first-line setting, platinum-based chemotherapy, which achieves objective response rates (ORR) in around 30% – 40% of NSCLC patients, may still be the best option for patients with EGFR wild-type (WT) tumours. However, molecular studies have indicated that certain mutations in exons 19 and 21 of the EGFR gene occur more frequently in patients who respond well to tyrosine kinase inhibitor (TKI) therapy. These mutations have become known as activating mutations. It has been observed that 70-90% of patients with these alterations respond to TKIs in the first-line setting.

In contrast, the efficacy of various treatments in the maintenance setting or in second-line of therapy is substantially lower, resulting in response rates (RRs) in around only 10% of patients.

Gefitinib (Iressa) is another EGFR TKI currently approved in EU Countries for treatment of patients with NSCLC and EGFR activating mutations independently of the line of therapy. Median PFS values reported with gefitinib (Iressa) in first line treatment of NSCLC are around 9.5-9.8 months [Paz Ares et al. 2009, IPASS study, Mok et al 2009].

3. 3. 1. Clinical Pharmacology

The clinical pharmacology program for erlotinib was extensively discussed in the original MAA and no new information is available for this extension of indication.

3. 3. 2. Clinical efficacy

- **The EURTAC study**

The MAH submitted the interim **Clinical Study Report ML20650 (EURTAC)** Trial

Methods

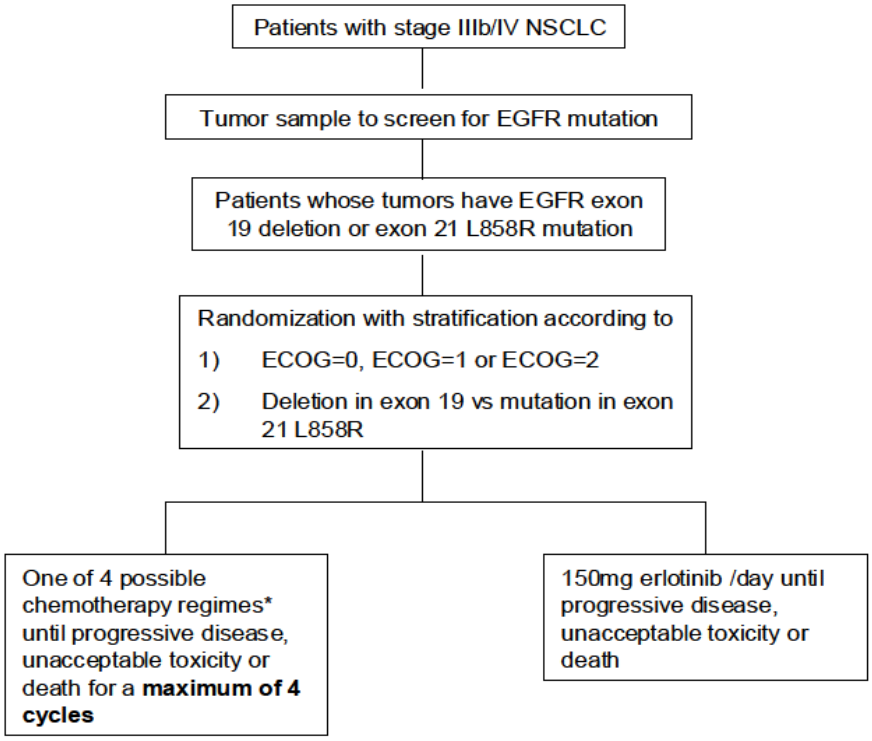
ML20650 (EURTAC) is a Phase III, multicenter, open-label,randomized study of erlotinib (Tarceva) treatment versus chemotherapy in patients with advanced non-small-cell carcinoma of the lung who present mutations in the tyrosine kinase (TK) domain of epidermal growth factor receptor (EGFR).

Randomised patients have been screened and confirmed exon 19 deletion or exon 21 L858R mutation in the EGFR TK domain. Tumour samples were screened for EGFR activating mutations by use of Sanger sequencing. Positive samples were confirmed using a PCR-based lab developed test with a sensitivity to detect 10% of mutant DNA in a background of 90% WT DNA.

Patients in the erlotinib arm received 150 mg/day orally until disease progression, unacceptable toxicity or death occurred. Patients in the chemotherapy arm received either a cisplatin plus docetaxel or a cisplatin plus gemcitabine regimen. Patients who were not candidates for cisplatin treatment would receive carboplatin instead.

The study design is presented in Figure 1.

Figure 1 Study Design



Study participants

After granting consent, patients with NSCLC were screened to detect EGFR-activating mutations.

Inclusion criteria

- Histologic diagnosis of NSCLC, stage IV or stage IIIB with malignant pleural effusion or N3 tumours not candidates for thoracic irradiation who present exon 19 deletions or an exon 21 L858R mutation in the TK domain of EGFR (histology was performed locally)
- Measurable or evaluable disease
- Patients over 18 years
- Performance status $\leq$2 on the ECOG scale
- Adequate bone marrow reserve, kidney and liver function
- Patients must be accessible for treatment and follow-up, capable of proper therapeutic compliance.
- Women of childbearing age must have a negative serum or urine pregnancy test before start
- Patients of both sexes including women who had their last menstrual period in the last 2 years to use a contraceptive method.
- Oral swallowing capability
- Absence of intestinal transit problems that could alter absorption of the medication

Exclusion criteria

- Women who are pregnant, lactating, presented a positive pregnancy test or who did not accept to undertake the test.
- Sexually active men and women (of childbearing age) who were not willing to use contraceptive methods during the study.
- Previous treatment with chemotherapy for metastatic disease. The administration of neoadjuvant or adjuvant chemotherapy was allowed as long as it was completed ≥ 6 months before entering the study.
- Previous treatment with therapeutic agents targeting EGFR.
- Patients could have received radiotherapy as long as the irradiated lesion was not the only target lesion for evaluating response and as long as radiotherapy had been completed before initiating the study treatment (a 2-week period was recommended).
- Treatment with an investigational drug agent during the 3 weeks before enrollment in the study.
- Any known significant ophthalmologic anomaly of the ocular surface. The use of contact lenses was not recommended.
- Pre-existent motor or sensorial neurotoxicity grade ≥ 2 according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) AE scale.
- Evidence of spinal cord compression.
- Incapacity to take oral medication or previous surgical procedures that affectabsorption and imply the need for intravenous or parenteral feeding.
- Other serious diseases or clinical conditions, including, but not limited to: Unstable heart disease ; History of significant neurologic or psychiatric disorders, ; Uncontrolled active infection ; Uncontrolled active peptic ulcer; Unstable diabetes mellitus or any other contraindication to corticoid use.; ASP/SGOT and/or ALT/SGPT > 1.5 × ULN associated to alkaline phosphatase > 2.5 × ULN.

- Absolute contraindication for steroid use.
- Dementia or significantly disturbed mental state that could interfere with the patient's understanding and granting of informed consent.
- History of another neoplasm other than carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason ≤ 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years.

Treatments

Erlotinib
Erlotinib was given at a dose of 150 mg/day once daily; the medication was to be taken at the same time every morning with 200 mL of water, at least 1 hour before or 2 hours after the ingestion of food. Patients received treatment until disease progression or unacceptable toxicity. For all practical effects a treatment cycle was defined as 3 weeks of continuous treatment with erlotinib.
Chemotherapy The following combinations of chemotherapy were allowed to be used per protocol:
• Cisplatin plus docetaxel: cisplatin 75 mg/m2 intravenous (i.v.) Day 1 and docetaxel 75 mg/m2 i.v.on day 1, repeat cycle repeated every 3 weeks
• Cisplatin plus gemcitabine: Cisplatin 75 mg/m2 i.v. on day 1 and gemcitabine 1250 mg/m2 on Days 1 and 8. Repeat cycles every 3 weeks. In the case of patients not eligible for treatment with cisplatin, cisplatin could be replaced by carboplatin. The schedules were the following:
• Docetaxel 75 mg/m2 day 1 and carboplatin AUC = 6 Day 1, every 21 days.
• Gemcitabine 1000 mg/m2 days 1 and 8 and carboplatin AUC = 5 Day 1, every 21 days.
When docetaxel was used, at each cycle prophylactic medication (6 doses of 8 mg of dexamethasone i.v.) was administered.

Tumour assessments

Tumour response was evaluated according to the RECIST version 1.0 criteria
Regular and symmetrical tumour assessments were performed by investigators. A blinded review was performed by an independent review committee (IRC).

Objectives

The objective of the EURTAC trial was to compare per oral treatment with erlotinib with standard chemotherapy regimens in the 1st line treatment of patients with advanced NSCLC and activating mutations in EGFR.

The primary objective of this study was to compare investigator-assessed PFS in the two treatment arms of the study (conventional chemotherapy vs. erlotinib) in patients with NSCLC in advanced stages (stages IIIB and IV) who have not received previous chemotherapy or any other systemic antitumor therapy for their disease and whose tumors have activating mutations in the TK domain of the EGFR.

The secondary objectives of this study were to assess:
• Investigator-assessed objective response
• Overall survival (including 1- and 2-year survival rates)
• Location of progression
• Safety profile
• Gene mutation analysis of EGFR in serum
• Quality of life (lung cancer symptom scale [LCSS])

Sample size - Interim Analysis

In the sample size calculation, conservative median PFS of 10 months was presumed for the erlotinib arm vs. 6 months in the chemotherapy arm. Standard statistical tests were used.

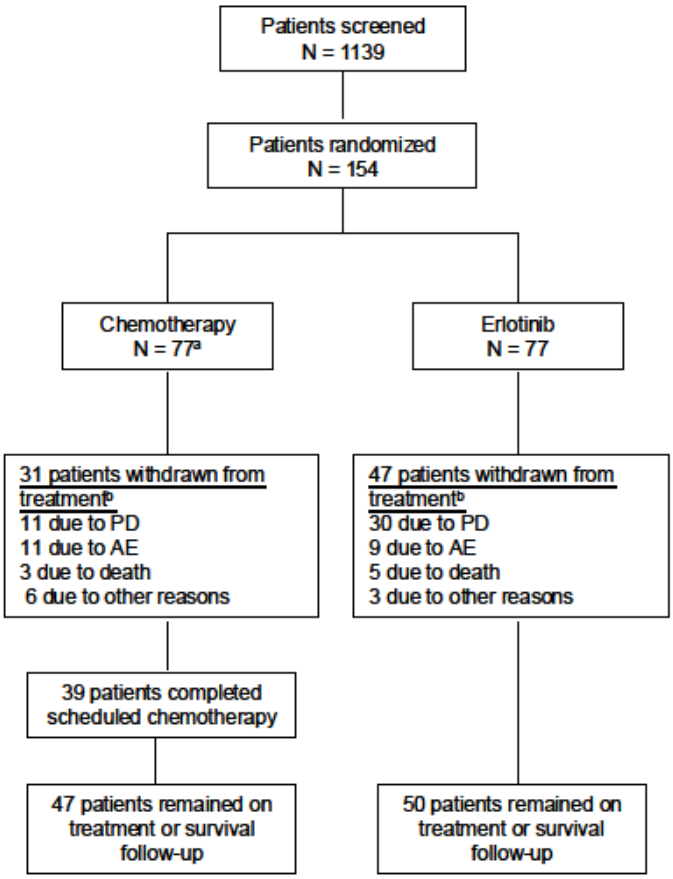
The planned sample size was 174 patients. An interim analysis was pre-specified after 88 out of 135 planned events had occurred. A Lan-DeMets alpha-spending function was used to maintain the significance level at 5%. A more conservative stopping boundary was introduced in the IDMC charter. The efficacy interim analysis was performed with a cut-off date of 2 August 2011.

Results

Disposition of patients

This study was conducted in Spain, Italy and France. The first patient was enrolled in 2007. At the time of the data-cut off for the interim analysis (2 August 2010) 154 patients had been randomized in the study: 77 received chemotherapy and 77 received erlotinib as 1st line treatment. The applicant has adequately accounted for the number of patients who were withdrawn from the study. Of note, the imbalances observed between the treatment arms in this respect can be explained by the longer treatment duration in the erlotinib arm (until progression) compared to the chemotherapy arm (for a maximum of 4 cycles (12 weeks).

Figure 2 Disposition of Patients



[a]One patient received chemotherapy prior to randomization

[b] The imbalance in the number of treatment discontinuations due to PD or death is due to the fact that chemotherapy was administered for a maximum of 4 cycles (12-week treatment) and erlotinib was administered until disease progression. At the time of cut-off for interim analysis, 27 patients had died in each arm and 47 and 45 PFS events were observed in the chemotherapy and erlotinib arm, respectively.

The applicant has adequately accounted for major protocol violations. The number is limited and is not considered to have affected the integrity of the trial.

Demographics

The majority of patients enrolled were from Spanish centers. As expected, more females were included in this trial (activating EGFR mutations are seen more frequently in females). All patients were Caucasians and the median age was 64 years. Small imbalances were observed between treatment arms regarding gender and smoking status. This is not considered critical.

Randomization was stratified by ECOG status and mutation type/location. These factors were well-balanced between treatment arms. Small imbalances in performance status were noted within the subgroups of different mutation type which is to be expected in subgroups.

Table 9 Summary of Demographic Data (FAS)

dm11_f Summary of Demographic Data
Protocol(s): ML20650 (W20650C)
Analysis: FULL ANALYSIS SET Center: ALL CENTERS

	CHEMOTHERAPY N = 76	ERLOTINIB N = 77
Age (years) at randomisation		
Mean	64.1	63.5
SD	9.39	10.77
SEM	1.08	1.23
Median	64.0	65.0
Min-Max	29 - 82	24 - 82
n	76	77
Age <65 (YES= <65, NO= >=65)		
YES	39 (51%)	38 (49%)
NO	37 (49%)	39 (51%)
n	76	77
Race (White vs. Other)		
WHITE	76 (100%)	77 (100%)
n	76	77
Sex		
FEMALE	60 (79%)	52 (68%)
MALE	16 (21%)	25 (32%)
n	76	77
Weight in kg		
Mean	64.66	68.40
SD	11.441	15.555
SEM	1.321	1.846
Median	62.00	65.00
Min-Max	49.0 - 102.0	42.0 - 119.0
n	75	71
Height in cm		
Mean	158.9	162.8
SD	8.43	9.27
SEM	0.97	1.12
Median	158.0	162.0
Min-Max	145 - 182	144 - 180
n	75	69
Smoking Status (derived)		
CURRENT SMOKER	10 (13%)	3 (4%)
NEVER SMOKED	56 (74%)	54 (70%)
PAST SMOKER	10 (13%)	20 (26%)
n	76	77
Country		
FRANCE	15 (20%)	20 (26%)
ITALY	6 (8%)	10 (13%)
SPAIN	55 (72%)	47 (61%)
n	76	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Smoking status (derived): a patient who stopped smoking since < 1yr is counted as current smoker.
Cut-off for statistical analysis: 02AUG2010
DM11 03FEB2011:20:40:46

Disease characteristics

As expected, most patients presented with adenocarcinomas with a small imbalance between the two treatment arms (88% of tumours in the chemotherapy arm vs. 95% in the erlotinib arm). The vast majority of patients had stage IV disease (> 90%).

Table 11 Summary of NSCLC History

dm16hist_f
Protocol(s): ML20650 (W20650C)
Analysis: FULL ANALYSIS SET Center: ALL CENTERS

	CHEMOTHERAPY N = 76	ERLOTINIB N = 77
Weeks since First Diagnosis of NSCLC		
Mean	22.45	21.83
SD	87.987	46.296
SEM	10.093	5.276
Median	5.00	5.29
Min-Max	0.9 - 727.9	1.6 - 211.3
n	76	77
Histology of NSCLC		
SQUAMOUS CELL CARCINOMA	-	1 (1%)
ADENOCARCINOMA	67 (88%)	73 (95%)
LARGE CELL CARCINOMA	1 (1%)	3 (4%)
OTHER	6 (8%)	-
BRONCHIOLOALVEOLAR CARCINOMA	2 (3%)	-
n	76	77
Stage of NSCLC at Baseline		
N3 NOT CANDIDATE FOR THORACIC RADIOTHERA	-	1 (1%)
STAGE IIIB (WITH PLEURAL EFFUSION)	5 (7%)	6 (8%)
STAGE IV (METASTATIC)	71 (93%)	69 (91%)
n	76	76[a]
Histopathological Grade of NSCLC at BL		
G1: WELL DIFFERENTIATED	4 (5%)	10 (13%)
G2: MODERATELY DIFFERENTIATED	17 (22%)	16 (21%)
G3: POORLY DIFFERENTIATED	15 (20%)	15 (19%)
G4: UNDIFFERENTIATED	1 (1%)	3 (4%)
GX: NON-EVALUABLE DIFFERENTIATION	-	3 (4%)
UNKNOWN	39 (51%)	30 (39%)
n	76	77

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Cut-off for statistical analysis: 02AUG2010
DM16 09FEB2011:20:51:16
[a] Note added by PDRD: Patient 111740/0033 did not have documented stage IIIb or stage IV NSCLC at baseline. Output modified to "Histology of NSCLC" instead of "History of NSCLC".

Primary endpoint: PFS (INV)
The duration of median follow-up was 10.7 months in the chemotherapy arm vs. 14.3 months in the erlotinib arm. At the time of the interim analysis, the data were reasonably mature: 92 events had occurred. Fourty seven (47) (61.8%) patients had an event in the chemotherapy arm vs. 45 (58.4%) in the erlotinib arm.

The HR for PFS as assessed by investigators was **0.42** (95% CI 0.27-0.64, p<0.0001) which corresponds to a 58 % reduction in the risk of progression or death. This is considered a highly clinically relevant gain in PFS. The K-M curves make a clear and early separation. The median PFS for patients in the chemotherapy arm was 5.2 months vs. 9.7 months in the erlotinib arm resulting in an absolute gain of 4.5 months in median PFS in erlotinib-treated patients.
12% of patients in the chemotherapy arm and 37% of patients in the erlotinib arm were event-free 1 year after randomization.

Table 14 Summary of PFS (FAS)

ettpfs_t_2000
Protocol(s): ML20650 (W20650C)
Analysis: Full Analysis Set

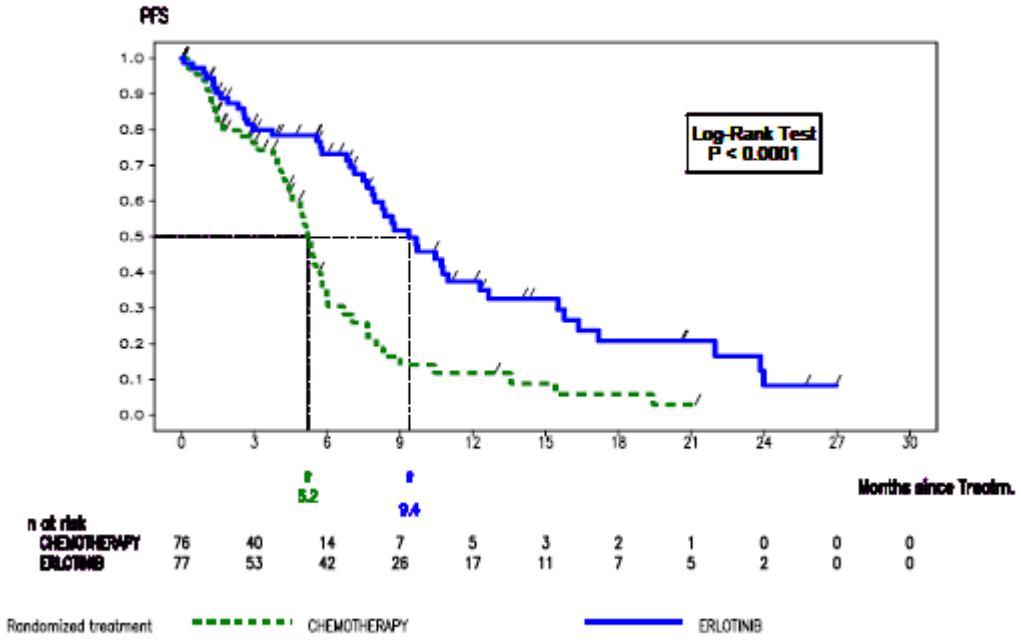
	CHEMOTHERAPY (N=76)		ERLOTINIB (N=77)
Patients with event	47 (61.8 %)		45 (58.4 %)
Patients without event*	29 (38.2 %)		32 (41.6 %)
Time to event (months)			
Median#	5.2		9.4
95% CI for Median#	[4.4;5.8]		[7.9;12.3]
25% and 75%-ile	3.2;7.7		5.7;16.4
Range##	0.0 to 21.2		0.0 to 26.9
p-Value (Log-Rank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

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

Program : $PROD/cd11677d/ml20650/ettpfs_t.sas
Output : $PROD/cd11677w/w20650c/reports/ettpfs_t_2000.out
03FEB2011 12:52

Figure 3 Kaplan-Meier Curve of PFS (FAS)

eratepfs_g_2000 Kaplan-Meier Curve of PFS
Protocol(s): ML20650 (W20650C)
Analysis: Full Analysis Set



Cut-off for statistical analysis: 02AUG2010

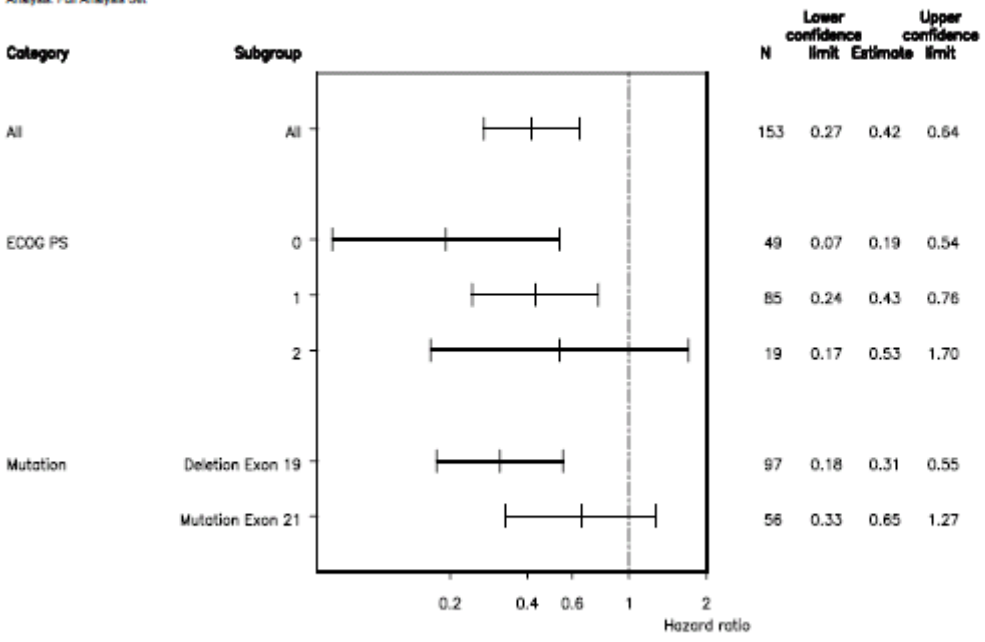
Program : $PROD/cd11677d/ml20650/eratepfs_g.sas / Output : $PROD/cd11677w/w20650c/reports/eratepfs_g_2000.cgm
03FEB2011 12:48

A number of relevant sensitivity analyses showed consistent results with the primary PFS analysis.

Subgroup analyses

Figure 4 Forest Plot of Hazard Ratios and 95% CIs for PFS by Subgroup (Stratification Factors)

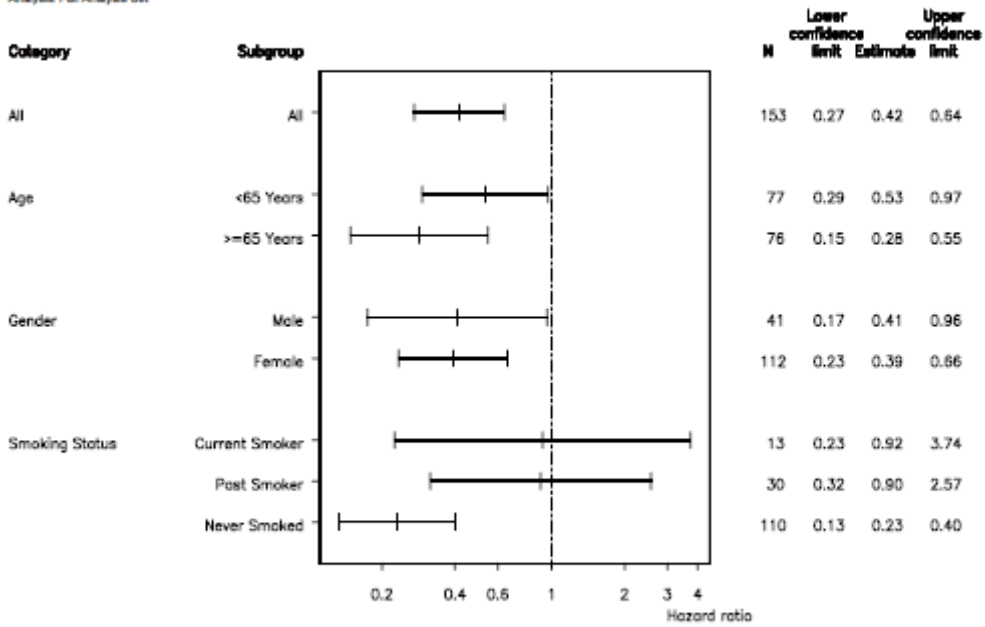
escopfas_g_2000. Forest Plot of Hazard Ratios and 95% CI for PFS by Subgroup (Stratification Factors)
Protocol[N]: BI(20650 (WZ0650C)
Analysis: Full Analysis Set



Cut-off for statistical analysis: 02AUG2010
Program: $PROD/cd11677d/mt20650/escopfas_g.sas / Output: $PROD/cd11677w/w20650c/reports/escopfas_g_2000.cgm
03FEB2011 12:56

Figure 5 Forest Plot of Hazard Ratios and 95% CIs for PFS by Subgroup (Demographic and Baseline Characteristics)

escopfadm_g_2000. Forest Plot of Hazard Ratios and 95% CI for PFS by Subgroup (Demographic and Baseline Characteristics)
Protocol[N]: BI(20650 (WZ0650C)
Analysis: Full Analysis Set



Smoking Status (derived): a patient who stopped smoking since < 1 yr is counted as current smoker.
Cut-off for statistical analysis: 02AUG2010
Program: $PROD/cd11677d/mt20650/escopfadm_g.sas / Output: $PROD/cd11677w/w20650c/reports/escopfadm_g_2000.cgm
03FEB2011 12:57

Most patients with activating EGFR mutations have adenocarcinomas. The subgroup of patients with non-adenocarcinomas was very small (n= 13) and only 1 patient had squamous cell histology.

IRC-based assessment of PFS

Not all scans have been reviewed by the IRC. The retrospective nature of the IRC review and logistic barriers are mentioned by the MAH as possible reasons for the incomplete review by the IRC. The percentages of scans reviewed in both treatments arms are relatively large during the first 30 weeks of treatment (where the number of patients is largest); 50-75% in the chemotherapy arm and 86-90% in the erlotinib arm.

Based on the number of available scans and relevant clinical information 30 patients were considered to have had an event by independent review in the chemotherapy arm vs. 31 patients in the erlotinib arm (data cut-off of 2 August 2010). The numbers were 47 and 45, respectively, in the analysis based on investigators' assessment. The HR for PFS (IRC) was **0.47** (95% CI: 0.28 - 0.78, p = 0.0030). The median PFS was 5.4 months in the chemotherapy arm vs. 10.4 months in the erlotinib arm. Even though this analysis is based on fewer events than the investigator-based analysis (64% of events in the chemotherapy arm and 69% of events in the erlotinib arm), this IRC-based result is consistent with the result of the primary analysis.

When focusing on patients with valid assessments by both investigator and IRC (46 patients in the chemotherapy arm and 61 patients in the erlotinib arm), the concordance rate was 63% in the chemotherapy arm and 75.4% in the erlotinib arm.

Figure 6 Kaplan-Meier Curve of PFS Asessment by the IRC

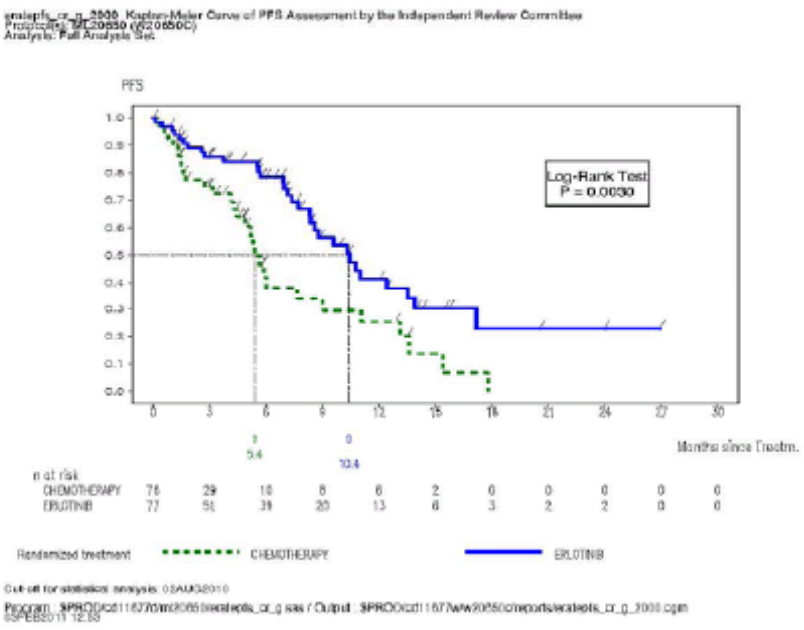


Table 16 Concordance Table of PFS Between the Investigator and the Independent Review Committee

econcpfs_t_2000
Protocol(s): ML20650 (W20650C)
Analysis: Full Analysis Set

	CHEMOTHERAPY N=76	ERLOTINIB N=77
n of patients (event or censored)	46	61
Concordance Rate *	29 (63.0%)	46 (75.4%)
Discordance in timing		
<1 week	35 (76.1%)	45 (73.8%)
1-<3 weeks	1 (2.2%)	1 (1.6%)
3-<6 weeks	1 (2.2%)	3 (4.9%)
6-<12 weeks	2 (4.3%)	4 (6.6%)
12-<24 weeks	3 (6.5%)	4 (6.6%)
24 weeks and more	4 (8.7%)	4 (6.6%)
n of events	18	24
Discordance in timing		
<1 week	16 (88.9%)	11 (45.8%)
1-<3 weeks	1 (5.6%)	1 (4.2%)
3-<6 weeks	-	3 (12.5%)
6-<12 weeks	-	3 (12.5%)
12-<24 weeks	-	4 (16.7%)
24 weeks and more	1 (5.6%)	2 (8.3%)

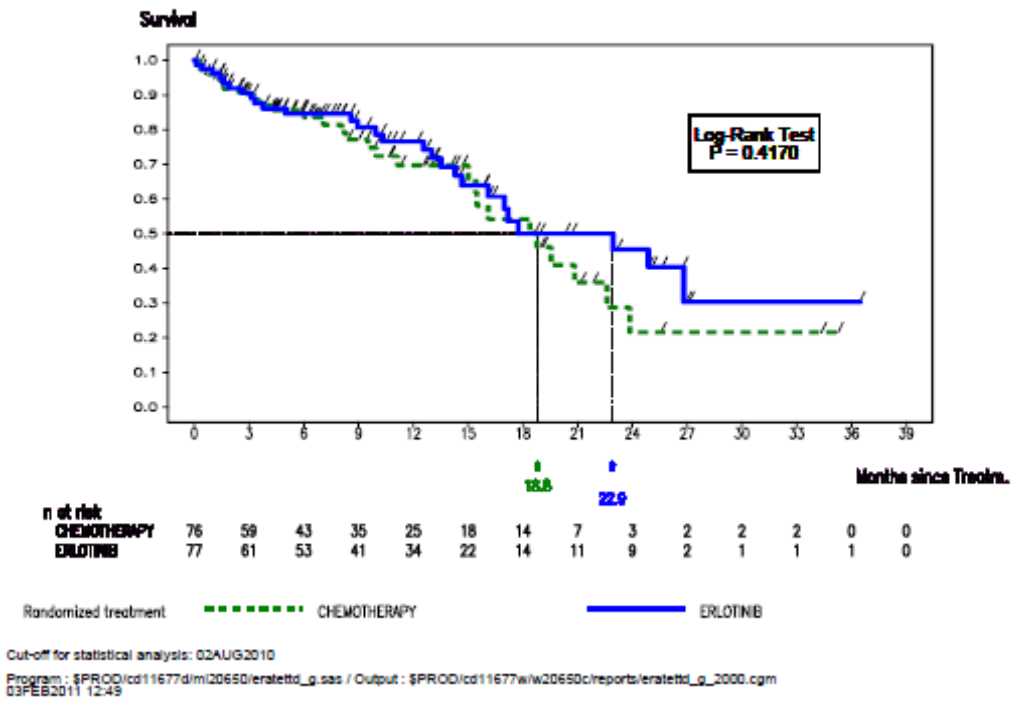
Percentages are based on n.
Only patients with a valid baseline and post-baseline assessment by the investigator or the IRC are included.
* Concordance stands for a) event IRC and event investigator
b) no event IRC and no event investigator
IRC: Independent Review Committee.
Cut-off for statistical analysis: 02AUG2010

Program : $PROD/cdl1677d/ml20650/econcpfs_t.sas / Output : $PROD/cdl1677w/w20650c/reports/econcpfs_t_2000.out
03FEB2011 12:55

OS

At the time of the interim analysis, only 35% of the patients had died reason why the OS data are considered still immature. The HR for OS was 0.80 (95% CI: 0.47 - 1.37, p-value 0.42). The median OS was 18.8 months in the chemotherapy arm vs. 22.9 months in the erlotinib arm.

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



At the time of the interim analysis more patients in the chemotherapy arm (67%) had received later lines of therapy (often including an EGFR, TKI) after progression vs. 36% in the erlotinib arm which will most certainly confound OS results.

Best Overall Response (CR/PR)

The percentage of responders (CR/PR) was significantly larger in the erlotinib arm (54.5%) compared with the chemotherapy arm (10.5%). Erlotinib-treated responders mainly experienced PR (51.9%).

Table 18 Summary of Best Overall Response (FAS)

ebor_t_2000 Summary of Best Overall Response
Protocol(s): ML20650 (W20650C)
Analysis: Full Analysis Set

	CHEMOTHERAPY (N=76)		ERLOTINIB (N=77)
Responders$	8 (10.5 %)		42 (54.5 %)
Non-Responders	68 (89.5 %)		35 (45.5 %)
95% CI for Response Rates*	[4.7; 19.7]		[42.8; 65.9]
Difference in Response Rates		44.02	
95% CI for Difference in Response Rates#		[30.2; 57.9]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		10.20	
95% CI for Odds Ratio		[4.32;24.08]	
Complete Response (CR)	0 (0.0 %)		2 (2.6 %)
95% CI for CR Rates*	[0.0; 4.7]		[0.3; 9.1]
Partial Response (PR)	8 (10.5 %)		40 (51.9 %)
95% CI for PR Rates*	[4.7; 19.7]		[40.3; 63.5]
Stable Disease (SD)	42 (55.3 %)		18 (23.4 %)
95% CI for SD Rates*	[43.4; 66.7]		[14.5; 34.4]
Progressive Disease (PD)	10 (13.2 %)		6 (7.8 %)
95% CI for PD Rates*	[6.5; 22.9]		[2.9; 16.2]
Missing (No Response Assessment)	16 (21.1 %)		11 (14.3 %)

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

Program : $PROD/cdl1677d/ml20650/ebor_t.sas
Output : $PROD/cdl1677w/w20650c/reports/ebor_t_2000.out
09FEB2011 12:45

In contrast, no significant difference was found between treatment arms in terms of disease control (= CR+PR+SD) (65.8% vs. 77.9%) based on investigators' assessment. This is due to the relatively high number of patients who experienced SD in response to chemotherapy.

QoL
Completion rates of the QoL questionnaire were too low to allow further analyses.

Updated Results
An additional post-hoc analysis was performed including additional data from period of time from cut-off for the planned interim analysis (August 2, 2010) until the date of disclosure of interim analysis results to study investigators (January 26, 2011). These data were presented at ASCO in 2011, and the Rapporteurs have specifically asked for these data to be presented in this submission.

The updated PFS analysis was performed when 111 events had occurred (67.8% in the chemotherapy arm and 60.5% in the erlotinib arm). The HR for PFS had further improved (= 0.37 95% CI: 0.25 – 0.54, p< 0.0001). The absolute gain in median PFS was unchanged (4.5 months) in erlotinib treated patients.

Table 6 Summary of PFS (FAS)

ettpfs_t_2000 Summary of PFS
Protocol(s): ML20650 (I20650G)
Analysis: Full Analysis Set

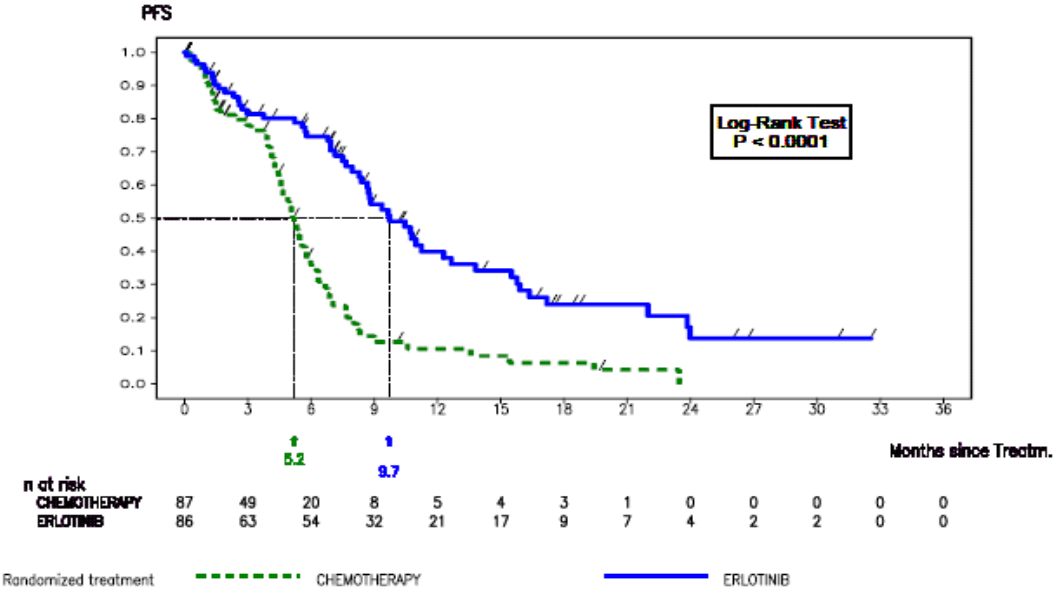
	CHEMOTHERAPY (N=87)		ERLOTINIB (N=86)
Patients with event	59 (67.8 %)		52 (60.5 %)
Patients without event*	28 (32.2 %)		34 (39.5 %)
Time to event (months)			
Median#	5.2		9.7
95% CI for Median#	[4.5;6.0]		[8.4;12.6]
25% and 75%-ile	3.8;7.0		5.8;17.2
Range##	0.0 to 23.5		0.0 to 32.5
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.37	
95% CI		[0.25;0.54]	
1 year estimate			
Patients remaining at risk	5		21
Event Free Rate#	0.11		0.40
95% CI for Rate#	[0.02;0.19]		[0.28;0.52]

PFS [months] (TTPFS_M) - Censoring: PFS Censoring (1=PD/death) (CSPFS)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 26JAN2011

Program : $PROD/cd11677d/ml20650/ettpfs_t.sas
Output : $PROD/cd11677d/i20650g/reports/ettpfs_t_2000.out
09MAY2011 8:50

Figure 1 Kaplan-Meier Curve of PFS (FAS)

eratepfs_g_2000 Kaplan-Meier Curve of PFS
Protocol(s): ML20650 (I20650G)
Analysis: Full Analysis Set



Cut-off for statistical analysis: 26JAN2011
Program : $PROD/cd11677d/ml20650/eratepfs_g.sas / Output : $PROD/cd11677d/i20650g/reports/eratepfs_g_2000.ogm
09MAY2011 8:51

OS results remain immature (40% of patients had died), but it is noteworthy that the HR for OS is no longer < 1. In contrast, the percentage of patients in the chemotherapy arm receiving further lines of

therapy and particularly crossing-over to receive erlotinib, had risen to 77% which is a possible explanation for the decreasing OS difference between treatment arms.

Supportive studies

An overview of data submitted as part of this application is provided in Table x.
Efficacy data are available from 438 patients with tumours having activating EGFR mutations, of who 234 received erlotinib as first-line therapy.

All studies reported, used erlotinib at the standard approved dose of 150 mg/day, which has already been established as a safe and efficacious dose in patients with advanced NSCLC.

Of note, reliability of these data presented as supportive couldn't be assessed by the CHMP as no clinical study report was submitted.

Table 4. Studies Supporting the Efficacy of Erlotinib in First-Line Treatment of NSCLC Patients with EGFR Mutations

- **Spanish Lung Cancer Group (SLCG) data (Rosell et al., N Engl J Med (2009)**

Methodology
The SLCG has conducted a prospective, large scale screening for EGFR mutations in patients with stage IIIB disease with pleural effusion or stage IV NSCLC. Patients were required to be chemotherapy-naïve or to have received up to two prior chemotherapy regimensRosell et al, 2009, to have measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST), and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2. Other eligibility criteria included availability of sufficient tumour tissue for EGFR mutation analysis, and adequate hematologic, renal and hepatic function. The smoking history of the patients was obtained at baseline, and patients were categorized as those who had never smoked (<100 lifetime cigarettes), former smokers (≥1 year since cessation), or current smokers (still smoking, or <1 year since cessation). Patients with active metachronous cancer, pulmonary fibrosis, severe heart disease or who were pregnant were specifically excluded.
A total of 2105 patients from 129 institutions in Spain were screened by a central laboratory for presence of EGFR mutations (exon 19 deletion and L858R substitution in exon 21) by polymerase chain reaction (PCR) and DNA sequencing Rosell, 2009 EGFR mutations were found in 350 / 2105 patients (16.6%) of which 217 received treatment with erlotinib. As expected, mutations were most frequent in women (69.7%), in never smokers (66.6%) and in patients with adenocarcinomas (80.9%).
The principal analyses were PFS and OS. In addition, post-hoc analyses included analyses of patients' characteristics and response according to sex, smoking history, age, ECOG PS, and treatment.
Included in the SLCG study were the data from TARGET, a prospective phase II trial of first-line erlotinib treatment in 43 chemo-naïve patients aged 18 years or older with histologically-documented diagnosis of advanced NSCLC with tumours with activating EGFR mutationsPaz-Ares, 2006. Patients had to have a WHO PS 0-2, normal organ function and no clinically relevant co-morbidities to be eligible for the trial. Eligible patients were allocated to receive erlotinib (150 mg/day) orally until PD or intolerable toxicity. Study assessments were performed every 3-4 weeks. The primary parameter of efficacy was TTP. Secondary parameters included RR, OS, QoL and toxicity profile.

Published Data Supporting First Line Erlotinib Single Agent Therapy in Patients with NSCLC and EGFR Mutations

Study Identifier / Type	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration; Duration of Erlotinib Treatment**	**Number of treated Patients with EGFR Mutations**	**Diagnosis**
Published Data Supporting First Line Erlotinib Single Agent Therapy in Patients with NSCLC and EGFR Mutations				
Spanish Lung Cancer Group (SLCG) Data Rosell et al. 2009	Open label, prospective, single arm, uncontrolled, feasibility study	Erlotinib 150 mg PO QD until disease progression or advent of intolerable adverse events	217 Erlotinib: 1st line: n = 113 2nd or further lines: n = 104	Previously treated or untreated stage IIIB with pleural effusion or stage IV NSCLC
Pooled analysis of Published Trials Paz-Ares et al. 2010	Pooled analysis of prospective or retrospective studies evaluating chemotherapy or single agent EGFR TKIs (erlotinib or gefitinib)	Erlotinib 150 mg PO QD Gefitinib 250 mg PO QD or 500 mg PO QD Platinum-based chemotherapy / docetaxel / standard chemotherapy	1809 Erlotinib (n = 365) 1st line: n = 70 2nd or further lines: n = 295 Gefitinib (n = 1069) 1st line: n = 520 2nd or further lines: n = 549 Chemotherapy (n = 375) 1st line: n = 359 2nd or further lines: n = 16	Previously treated or untreated NSCLC and EGFR mutations
Oral Presentations and Meeting Abstracts of Studies in Patients with NSCLC and EGFR Mutations Receiving Erlotinib Single Agent Therapy				
CALGB30406 Janne et al, 2010	Randomized, active controlled, parallel group study	Erlotinib 150 mg PO QD 6 cycles of platinum-based chemotherapy: carboplatin (AUC = 6) / paclitaxel 200 mg/m2 plus erlotinib 150 mg PO QD	67 Erlotinib: n = 32 Chemotherapy plus erlotinib: n = 35	Previously untreated patients with stage IIIB/IV NSCLC
Laskin et al. 2009	Open label, prospective, single arm, uncontrolled, feasibility study	Erlotinib 150 mg PO QD until disease progression	19	Previously untreated stage IIIB/IV NSCLC patients
Controlled Clinical Trials in Patients with NSCLC and EGFR Mutations Receiving Erlotinib Single Agent Therapy				
SATURN (BO18192)	Multi-center, randomized, double-blind, placebo-controlled study	Erlotinib 150 mg PO QD until disease progression or advent of intolerable adverse events following 4 cycles of platinum-based chemotherapy	49Erlotinib: n = 22 Placebo: n = 27	Previously treated patients with stage IIIB/IV NSCLC

Results

Only 296 patients were considered eligible for erlotinib treatment at a dose of 150 mg/day until PD or intolerable toxicity. Further 79 patients did never receive treatment for a variety of reasons including death (n = 18), patient or physician decision (n = 23), or received erlotinib treatment subsequent to the analysis (n = 38). Therefore, a total of 217 patients received treatment with erlotinib (150 mg/day) and were included in the analysis. In these remaining patients, median age was 67 (22-88) years. 72.8% of subjects were female, 98.2% were Caucasian, 68.2% were never smokers and 76.5% had an ECOG PS of 1 or 2. Regarding tumour type, 81.1% of tumours were adenocarcinoma.

Of these patients, 113 (52.1%) received erlotinib as first-line therapy, and 104 received erlotinib as second- or third-line therapy. Median follow-up for all patients was 14.0 months (range 1 to 42 months).

Median PFS in the overall population (N = 217) was 14.0 months (95% CI, 11.2 to 16.7) and was comparable in patients receiving first-line therapy (14.0 months, 95% CI, 9.7 to 18.3; N = 113) and second- or further line therapy (13.0 months; 95% CI, 9.7 to 16.3; N =104).
Of the 197 patients who could be evaluated for response, 24 had a complete response (CR), 115 had a partial response (PR), 38 had SD and 20 had PD. The overall rate of CR or PR to erlotinib was 70.6%.
At the time of the analysis, median OS in the overall population was 27.0 months (95% CI, 22.7 to 31.3 months). Similar results were found in patients who received erlotinib as first-line therapy (28.0 months: 95% CI, 22.7 to 33.0 months) or as second-line therapy (27.0 months: 95% CI, 19.9 to 34.1 months).

There were no significant differences in PFS according to performance status, age, smoking history, or type of EGFR mutation (Table 2). However, median PFS was shown to be longer in females (16.0 months: 95% CI, 12.7 to 19.2 months) than in males (9.0 months: [95% CI, 6.1 to 11.9 months]; p = 0.003). Similarly, median OS was 29.0 months (95% CI: 24.9 to 33.1) in females and 18.0 months (95% CI: 14.5 to 21.5) in males (p = 0.05) in these patients with activating EGFR mutations. The multivariate analysis revealed an association between poor PFS and male sex and the presence of the exon 21 (L858R) mutation.

- **Pooled Analysis of Published Clinical Trial Data (Paz-Ares et al., J. Cell. Moll. Med. Vol 14, N01-2, 2010 pp. 51-69)**

Methodology:
In this literature review, the medical literature (Medline, Biosis Previews and Embase) was reviewed to identify appropriate clinical studies for inclusion in the pooled analysis. The search was limited to studies published in 2004 or later and non-English language manuscripts and reviews were excluded. In addition, studies presented at the American Society of Clinical Oncology (ASCO) meetings in 2008 and 2009 were reviewed as well. Studies that were performed in the maintenance or adjuvant treatment settings or involved sequential administration of multiple EGFR TKIs were excluded from the pooled analysis.

Within the studies included in the pooled analysis, a variety of techniques were used to determine the EGFR mutation status of tumours. However, the methods used in individual studies were not critically assessed as part of the pooled analysis.

PFS (or time to progression [TTP]) was chosen as the most appropriate endpoint to evaluate between studies and the main focus of the analysis was to obtain an estimate of the pooled median PFS by a weighted average of the single study medians. Median PFS estimates obtained in each eligible study were summed and the pooled median PFS estimated as the group-size weighted average.

Since many reports did not provide information on line of therapy specifically for patients with tumours having EGFR mutations, the outcome has not been assessed according to line of therapy in the pooled analysis. However, in order to estimate the effect of treatment in the first-line setting, an analysis was

performed that included only studies where 90% or more of the included patients (regardless of EGFR mutation status) received the treatment in question as first-line therapy (in consequence, the Spanish SLCG study was not included in this subgroup analysis.)

Results:
A total of 12 studies involving 365 patients evaluated erlotinib, 39 studies involving 1069 patients evaluated gefitinib and 9 studies involving 375 patients evaluated chemotherapy. Among the studies included in the pooled analysis, the estimated proportion of patients who received first-line treatment with erlotinib, gefitinib and chemotherapy was 57%, 57% and 95%, respectively.

For patients treated with any line of therapy, median PFS was 13.2 months (range 8.6 to 15.8 months) in patients treated with erlotinib compared to 9.8 months (range 3 to 16 months) in patients treated with gefitinib and 5.9 months (range 4 to 8.4 months) in patients treated with chemotherapy.

In the weighted pooled analysis, the overall median PFS was determined as 13.2 months (95% Accuracy Interval [AI], 12.0 to 14.7 months) for erlotinib treated patients, 9.8 months (95% AI, 9.2 to 10.4 months) for gefitinib treated patients and 5.9 months (95% AI, 5.3 to 6.5 months) for patients treated with chemotherapy.

For patients treated predominantly in the first-line setting, median PFS was 12.5 months (range 10.0 – 16.0 months) in patients treated with erlotinib compared to 9.9 months (range 9.0 – 10.9 months) in patients treated with gefitinib and 6.0 months (range 4.5 – 6.7 months) in patients treated with chemotherapy.

- **CALGB30406 Phase II study (Janne et al., J Clin Oncol 28:7s, 2010)**

Methodology

The CALGB30406 study was a randomized Phase II trial designed compared to the first-line therapy with erlotinib alone in combination with carboplatin/paclitaxel in chemotherapy-naïve patients with advanced NSCLC, never or light smokers.

Patients were selected on the basis of smoking history (never or light smokers) and randomized to erlotinib (150 mg/day) or 6 cycles of carboplatin (AUC = 6) / paclitaxel (200 mg/m^2) plus erlotinib (150 mg/day) followed by single agent erlotinib. Collection of pre-tumour assessments was mandatory for determination of EGFR mutation status. The primary endpoint was PFS. Secondary endpoints included RR and OS.

Results

The results of the CALGB30406 study were reported at ASCO in 2010. Of the 182 patients randomized, 105 were identified to have tumours with wild-type EGFR and 67 were identified to have tumours with activating EGFR mutations (32 who received erlotinib alone and 35 who received chemotherapy plus erlotinib).

Female patients comprised 61% and 58% of the studied population, respectively, and the majority were Caucasian (76% and 84% in the erlotinib-carboplatin and erlotinib alone arms, respectively). Most patients (>75% in both arms) were never smokers and the majority had adenocarcinoma subtype (87% in the erlotinib-carboplatin arm vs 80% in the erlotinib alone arm).

Overall, PFS was similar between the erlotinib (6.7 months; [80% CI, 4.7 to 8.2 months]) and chemotherapy plus erlotinib (6.0 months; [80% CI, 5.6-7.3 months]) treatment arms, respectively. However, in patients with tumours with activating EGFR mutations, PFS was increased in both erlotinib treatments arms (16.4 months; [80% CI, 12.1 to 23.8] and 17.2 months [80% CI, 11.1 to 27.6] in the erlotinib alone and chemotherapy plus erlotinib arms, respectively).

Consistent with results for PFS, in patients with tumours with activating EGFR mutations, OS was increased in both erlotinib treatment groups. In patients who received erlotinib single agent therapy, OS was 27.6 months [80% CI; 24.0 to 42.8 months]. Similarly, OS in patients who received combination therapy was 39.0 months [80% CI: 39.0 - not reached].

In patients with tumours with EGFR mutations who received erlotinib alone, RR was 66%. In patients treated with erlotinib plus chemotherapy, RR was 69%.

- **Phase II study (Laskin et al. 2009)**

Methodology

This Phase II clinical trial of first-line erlotinib for clinically selected patients with advanced NSCLC showed the feasibility of performing pre-treatment biopsies in this clinical setting. The patient population enrolled was 'enriched' in that patients were selected for at least two of the following: never smokers, female gender, Asian/Southeast Asian origin, and BAC or adenocarcinoma. A total of 65 patients with advanced (Stage IIIB/IV) NSCLC, no prior chemotherapy for advanced disease and an ECOG PS $\leq$ 2 were selected to receive erlotinib 150 mg/day until PD. The primary endpoint of the trial was non-progression at 8 weeks.

Results

More than 80% of patients were female, 75% were never smokers, 70% were of Asian origin and 69% had adenocarcinoma subtype. Results of a mutational analysis showed that of the 49 samples with adequate DNA for analysis, 19 (39%) had EGFR mutations (exons 19 and 21). Seventeen of these patients were of Asian ethnicity and 18 were never smokers.

Clinical results showed that 52 of the patients treated with erlotinib (80%) had not progressed after 8 weeks. Female patients, patients who were never smokers, patients with adenocarcinoma histology and patients of Asian ethnicity were more likely to derive benefit from erlotinib treatment. PR was observed in 22 patients (34%) and SD in 24 patients (37%) with a disease control rate of 71%. Of the 22 patients with a PR, 17 had tumours with activating EGFR mutations. Two of the 24 patients with SD had tumours with activating EGFR mutations. TTP in patients with tumours with EGFR mutations was 12.8 months and median OS was 17.0 months in patients with tumours with EGFR mutations.

- **Study BO18192 (SATURN)**

Methodology

This is a multi-centre, double-blind randomized Phase III study designed to evaluate the efficacy of erlotinib or placebo following 4 cycles of platinum-based chemotherapy in patients with histologically documented, advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC who have not experienced disease progression or unacceptable toxicity during chemotherapy.

After eligibility screening, patients with Stage IIIB or IV NSCLC completed 4 cycles of an acceptable platinum-based chemotherapy combination. Following chemotherapy, patients who met the following criteria; ECOG PS of 0 – 1, a life expectancy of at least 12 weeks, adequate haematological, renal and

hepatic function, and absence of unacceptable toxicity and/or disease progression (CR, PR or SD), were considered eligible for erlotinib treatment.

Eligible patients were randomized to receive either erlotinib 150 mg/day or placebo until PD, unacceptable toxicity or death. Randomization was performed using an adaptive minimization method which ensured a balanced stratification by treatment arm for the following factors: EGFR protein expression by IHC, stage of disease at start of chemotherapy, ECOG PS, chemotherapy regimen, smoking status and region. Treatment was to continue until PD, unacceptable toxicity or death.

Mandatory tumour sampling was performed at screening. Tumour measurements (RECIST) were conducted at screening, baseline, every 6 weeks until week 48 and then every 12 weeks until PD. QoL was assessed using the Functional Assessment of Chronic Illness Therapy - Lung (FACT-L) instrument.

The co-primary efficacy endpoints were investigator-assessed PFS according to RECIST in all patients and in the EGFR IHC positive population. An independent combined radiological and clinical assessment was undertaken to provide an independent assessment of response and PD. Secondary efficacy endpoints included OS in all patients, OS in EGFR IHC positive population, PFS in EGFR IHC negative subgroup, OS in EGFR IHC negative subgroup, TTP, time to symptom progression, response rates (RECIST) and QoL. Exploratory analyses of other molecular markers and their correlations with clinical outcomes were conducted.

With the exception of EGFR status assessment by IHC, other biomarkers were investigated to generate hypotheses regarding their potential value as predictive indicators of clinical benefit from erlotinib therapy in NSCLC. Those biomarkers included EGFR gene copy number by fluorescence *in situ* hybridization (FISH), EGFR mutation status, Kirsten Rat Sarcoma 2 viral oncogene homolog (K-ras) mutation status, and the status of a polymorphism in EGFR Intron 1. Subgroup analyses of these biomarkers were pre-specified in the statistical analysis plan.

Results

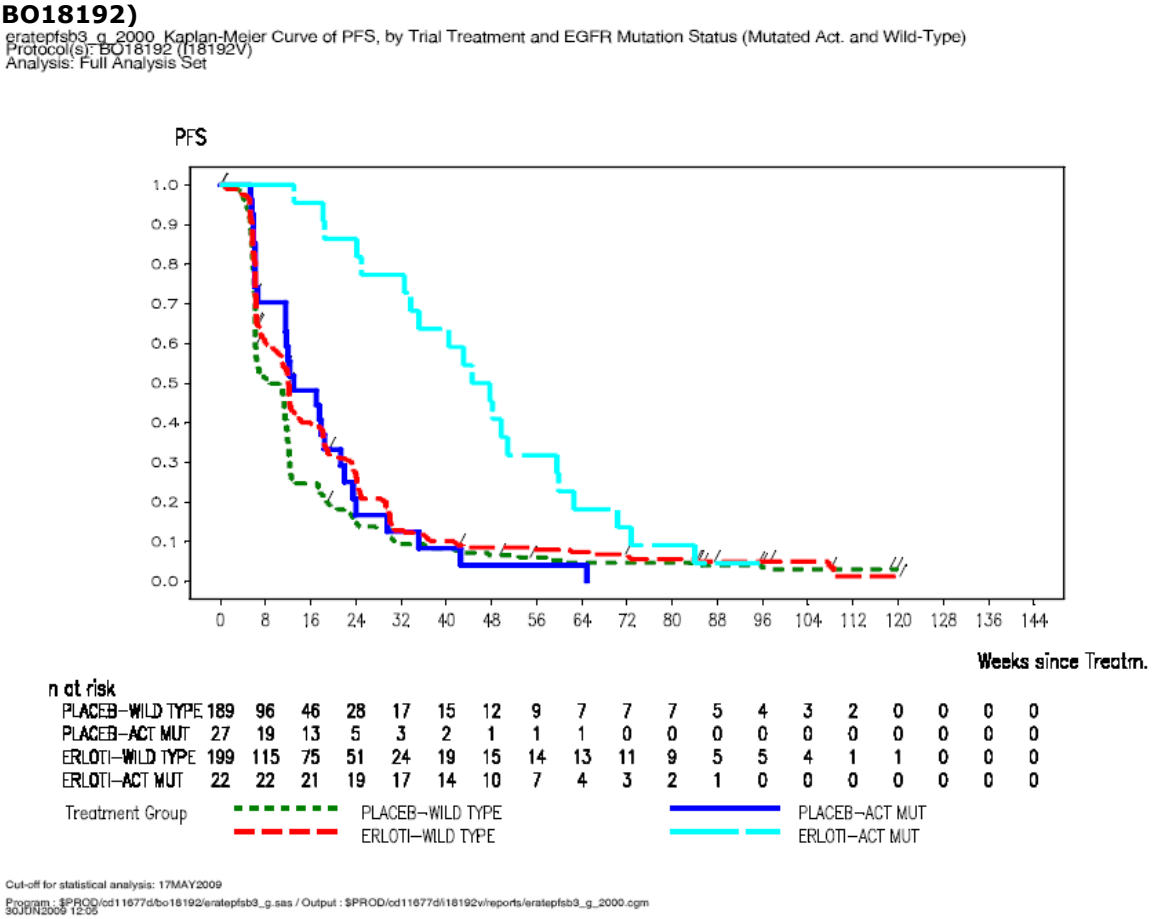
Patients were randomized to treatment with erlotinib (150 mg/day) (n = 438) or placebo (n = 451) until PD or intolerable toxicity.

In patients with a known EGFR mutation status (n = 449), 11% were identified with mutation positive tumours, 22 in the erlotinib group and 27 in the placebo group.

Data presented for study BO18192 are from the clinical cut-off for overall survival (May 17, 2009) since this is the most recent data.

In patients with tumours with activating EGFR mutations, addition of erlotinib after 4 cycles of chemotherapy significantly improved PFS compared with placebo (HR 0.23, [95% CI, 0.12 to 0.45]; log-rank $p < 0.0001$). Median PFS was 46.1 weeks, [95% CI, 33.7 to 59.6] in the erlotinib arm compared with 13.0 weeks the placebo arm [95% CI, 11.6 to 21.3]. The Kaplan-Meier curve for PFS is presented in figure 9.

Figure 9. Kaplan-Meier Curves of PFS by Trial Treatment and EGFR Mutation Status (Study BO18192)



Both patients with EGFR mutated and WT tumours benefited from treatment with erlotinib (Table 3).

Table 3. Summary of PFS in the EGFR Mutation Positive Subgroup (Study BO18192)

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

The HR was 0.78 [0.64; 0.96] (p=0.0182) in patients with WT tumours treated with erlotinib compared to placebo. In the EGFR WT population, median PFS in patients receiving erlotinib was 12.0 weeks

(95% CI, 10.9 to 12.7 weeks) compared with a median PFS of 8.9 weeks (95% CI, 6.3 to 11.4 weeks) in patients receiving placebo (Table 4).

Table 4. Summary of PFS in the EGFR WT Subgroup (Study BO18192)

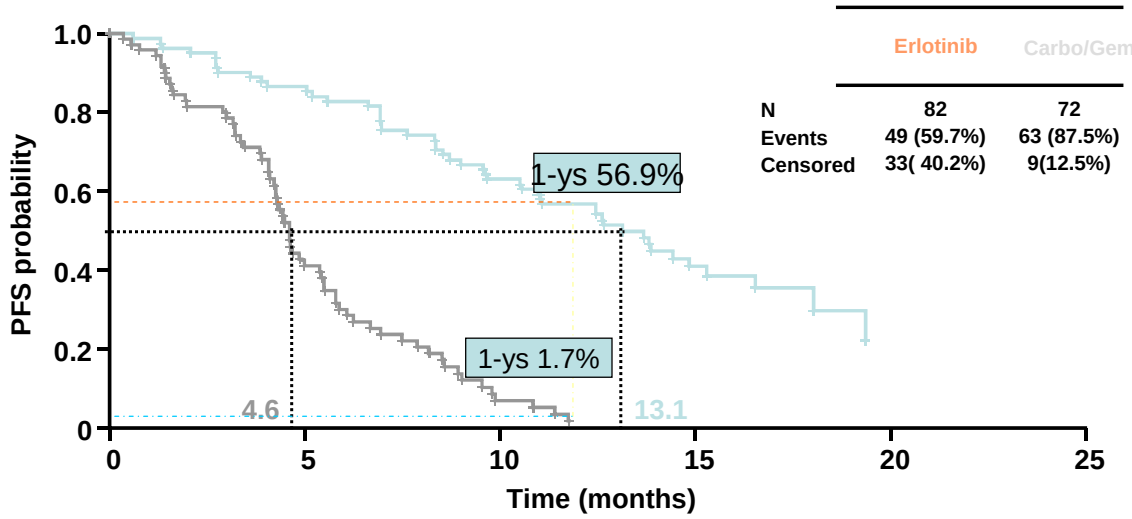
	PLACEBO (N=189)	ERLOTINIB (N=199)
Patients with event	179 (94.7 %)	184 (92.5 %)
Patients without event*	10 (5.3 %)	15 (7.5 %)
Time to event (weeks)		
Median#	8.9	12.0
95% CI for Median#	[6.3;11.4]	[10.9;12.7]
25% and 75%-ile	6.0;13.3	6.1;24.1
Range##	0.1 to 119.7	0.1 to 120.3
p-Value (Log-Rank Test)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

- **Study ML20981 (OPTIMAL)**

OPTIMAL study is an ongoing randomized, multicenter Phase III investigator sponsored trial (IST) conducted in China comparing efficacy and safety of first-line erlotinib versus carboplatin plus gemcitabine chemotherapy in NSCLC patients with tumours with activating EGFR mutations. This study was a trial sponsored and run by the Chinese Thoracic Oncology Group (CTONG). Since no CSR is available for this study, the MAH submitted the overview of the efficacy results as part of the responses to the 1st RfSI and as they have been presented at international congresses:

Of 549 patients screened, 186 (34%) had *EGFR* activating mutation NSCLC, 165 were randomized and 154 included in the study population (82 erlotinib; 72 carboplatin/gemcitabine [carb/gem]). Baseline data were well-balanced between the erlotinib and carb/gem arms: male (42% vs. 40%, respectively), adenocarcinoma (88% vs. 86%), never-smoker (72% vs. 69%) and type of *EGFR* activating mutation (exon 19 deletion: 52% vs. 54%). The median PFS was 13.1 months in the erlotinib group compared with 4.6 months in the carb/gem group; PFS HR = 0.16 [95% CI, 0.10 to 0.26]; p <0.0001 (Figure 10).

Figure 10. Progression-Free Survival in the OPTIMAL Study



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

Overall, the studies enrolled patients with advanced NSCLC (stage III/IV), median age ranged between 22 and 88 years and more than 80% of patients in the studies had an ECOG PS <2. Adenocarcinoma was the most common tumour subtype and the majority of patients in each of these studies were females who had never been smokers.

An overview of efficacy results for the erlotinib studies in NSCLC patients with tumours having activating EGFR mutations is shown in Table 5.

Table 5. Summary of Efficacy Results from Erlotinib Trials in Patients with Tumours Having EGFR Mutations (Evaluable Patients)

Parameter	SLCG Data[a]	Paz-Ares Pooled Analysis		CALGB30406		Laskin et al	Study BO18192[e]	
		Chemo	Erlotinib	Erlotinib plus C-P	Erlotinib Alone		Placebo	Erlotinib
	N = 217	N = 375	N = 365	N = 35	N = 32	N = 19	N = 27	N = 22
Median PFS/TTP* (months)	14.0 **14.0**[b] (n = 113) 13.0[c] (n = 104)	5.9 **6.0** [d] (n = 359)	13.2 **12.5**[d] (n = 70)	17.2	16.4	12.8*	3.0	10.6
Hazard Ratio [95% CI]	-	-	-	-	-	-	0.23 [0.12-0.45] p < 0.0001	
Median OS (months)	27.0 **28.0**[b] (n = 113) 27.0[c] (n = 104)	N/A	N/A	39.0	27.6	17.0	23.8	NR
Hazard Ratio [95% CI]	-	-	-	-	-	-	0.83 [0.34; 2.02] p = 0.6810	
Response Rate	70.6%	N/A	N/A	69%	66%	-	3.7%	50%
CR	12.2%	-	-	N/A	N/A	-	0	45.5%
PR	58.4%	-	-	N/A	N/A	89.5%	3.7%	40.9%
SD	19.3%	-	-	N/A	N/A	10.5%	66.7%	50%
PD	10.2%	-	-	N/A	N/A	-	29.6%	0

[a] The SLCG study was included in the review of published trials (Paz-Ares et al, 2010) and the overall median PFS was included in the analysis of a weighted pooled PFS for this study. However, the study was not included in the

analysis of PFS in predominantly first-line patients as the population comprised 52% of patients who received first-line therapy and 48% of patients who received erlotinib as second- or third-line therapy.
[b] median PFS or OS in patients receiving first-line therapy.
[c] median PFS or OS in patients receiving second or third line therapy.
[d] □median PFS in studies in which 90% of patients received treatment in the first-line setting (predominantly first-line patients).
[e] Data from the study BO18192 cannot be compared directly with the other 1st-line data presented in this table, because the treatment in this study was given as maintenance therapy after end of chemotherapy in a subset of responding patients and the time to event was measured only from end of standard first line therapy.

Due to the marked differences in study design and variety of data sources, no pooling of the study data has been performed.

Discussion on clinical efficacy

The applicant has submitted the CSR of the interim results from study ML 20650 (EURTAC), a randomised Phase III, open-label trial designed to evaluate the efficacy and safety of erlotinib treatment in previously untreated patients with advanced NSCLC who present mutations in the tyrosine kinase domain of EGFR.

The EURTAC study is the first prospectively conducted, relatively large randomized, unblinded phase III trial comparing the efficacy of erlotinib to a standard platinum-based doublet regimen in the 1st line treatment of patients with EGFR activating mutations in Europe. Erlotinib was dosed at 150 mg/day which is the dose already approved for 2nd line and maintenance treatment. Standard doses were used in the chemotherapy regimens. The control arm is acceptable: 4-6 cycles of platinum-based doublets represent the standard regimen in the first-line treatment of advanced NSCLC. The choice of the specific chemotherapy regimen was at the discretion of the treating physician (4 options were pre-specified). In case of AEs, recommendations for dose reductions/interruptions had been pre-specified for both erlotinib and chemotherapy regimens.

Following review of the interim analysis results, the IDMC recommended stopping of the trial after demonstration of a substantial benefit of erlotinib over chemotherapy. At the time the HR for PFS was 0.42 (95% CI 0.27-0.64, p<0.0001) which corresponds to a 58 % reduction in the risk of progression or death. The K-M curves make a clear and early separation. The median PFS for patients in the chemotherapy arm was 5.2 months vs. 9.7 months in the erlotinib arm resulting in an absolute gain of 4.5 months in median PFS in erlotinib-treated patients. This is lower than what was observed for erlotinib as first-line treatment in the study by Rosell et al. (14 months (95% CI: 11.2 – 16.7)) and in the meta-analysis by Paz-Ares et al. (12.5 months). A relatively higher degree of patients with tumour stage IV (>91%) and other prognostic factors of poor outcome (males, previous smokers, pre-treated patients, mutation type, poor PS) might explain the poorer result in the present study. This being an interim analysis may also be a possible cause. Nevertheless, this is still considered a highly clinically relevant gain in PFS. The robustness of the result was confirmed in a number of sensitivity analysis and consistent results were found in subgroups with an acceptable sample size.

The trial was unblinded due to the different nature and schedules of the treatment arms: The control arm was represented by 4 cycles of standard platinum-based doublets vs. the test arm of continuous dosing of erlotinib until progression, death or unacceptable toxicity whichever occurred first. The primary endpoint was PFS which is acceptable in the 1st line setting. Secondary endpoints were ORR, OS, safety, QoL (LCSS scale), location of progression and gene mutation analyses of EGFR. Furthermore, IRC-based assessments of PFS and ORR were introduced in order to rule out investigator-related bias which is endorsed.

Due to the unblinded nature of the trial an independent blinded review was introduced by an IRC. Concordance rates observed between investigators' review and the IRC were 63-73%. More scans were reviewed in the erlotinib arm and there is some uncertainty left as to the reason for this

discrepancy. However, overall the percentages of scans reviewed in both treatment arms are relatively large. Therefore, the risk of a large systemic bias in the investigators' assessments can be ruled out. The HR for PFS (IRC-based) was 0.47 (95% CI: 0.28 - 0.78, p = 0.0030) and the median PFS 5.4 months in the chemotherapy arm vs. 10.4 months in the erlotinib arm, thus confirming the result of the INV-based analysis.

A significant increase in patients experiencing a PR/CR (mainly PR) was seen in patients treated with erlotinib (54.5%) compared to chemotherapy (10.5%). The observed RR in the erlotinib arm was generally lower than previously observed (70% in the Rosell study). The same explanations as offered for PFS may apply here. Furthermore, patients with "evaluable" disease and not only "measurable" disease were allowed in the study (8 in the erlotinib arm). These patients can't obtain documentation of PR by RECIST.

OS results were immature. So far no difference in OS was observed between treatment arms but a high degree of cross-over and later lines of therapies are expected to have confounded the OS results. Mature OS data must be submitted as a FUM.

QoL data are inconclusive due to low completion rates.

An updated analysis was performed when 111 PFS events had occurred (67.8% in the chemotherapy arm and 60.5% in the erlotinib arm). The HR for PFS had further improved (= 0.37 (95% CI: 0.25 – 0.54, p< 0.0001). The absolute gain in median PFS was unchanged (4.5 months) in erlotinib treated patients. OS results remain immature (40% had died), but it is noteworthy that the HR for OS is no longer < 1. In contrast, the percentage of patients in the chemotherapy arm receiving further lines of therapy and particularly crossing-over to receive erlotinib had risen to 77% which is a possible explanation for the decreasing OS difference between treatment arms.

Overall, the updated results confirmed the results of the original interim analysis.

The MAH submitted in the original application data derived from published subgroup analyses of three phase II-III studies. These studies involved a very limited number of NSCLC patients with known EGFR activating mutations. The pooled analysis of recent trials performed in patients with EGFR activating mutation tumours treated with first-line chemotherapy or with EGFR TKIs (erlotinib and gefitinib) was hampered by the same flaw. No study reports were submitted allowing an assessment of the reliability and quality of the data.

From a clinical perspective the data presented on erlotinib were considered of clinical relevance. The results consistently show median PFS advantages with erlotinib in first line treatment of NSCLC patients with EGFR activating mutations ranging from 12.5 up to 16.4 months. Such results are of clinical relevance in this patient population. Such patients historically are known to progress after a median of 6 months when treated with currently recommended 1st line platinum-based chemotherapy and, otherwise, after a median of 10 months when treated with gefitinib (IPASS study). The survival results of the SLCG study, and of the CALGB30406 study, showing a median OS with erlotinib of 28 and 27 months respectively, would confirm the benefits of erlotinib in the target population.

The results indicate that patients with NSCLC and activating EGFR mutations represent a distinct subgroup of patients and that these activating mutations in the EGFR are a strong predictive marker of response to TKIs. Furthermore, there's a molecular rationale behind this marked response which has been reproducible in several trials.

However, from a regulatory perspective, the lack of CSRs from prospectively conducted trials in the first-line treatment of patients with advanced NSCLC and EGFR mutation positive tumours was considered a major deficiency in the original application. The databases were not designed for regulatory purposes and the data quality and GCP compliance could not be evaluated. The main endpoints PFS and RR in these open-label multicenter studies are much more prone to bias than e.g.

OS. Due to the complexity of the assessment of PFS and the risk of bias, the CHMP has issued the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man on methodological aspects of PFS. If and to what extent these considerations were followed cannot be evaluated without full CSRs.

Finally, availability of other licensed EGFR TKI such as gefitinib for treatment of NSCLC limits the medical need for this class of drugs in this subgroup of the NSCLC population. Indeed, although in several *in vitro* studies certain EGFR mutations appear to be more sensitive to erlotinib than gefitinib, confirming prospective clinical data comparing activity of gefitinib versus erlotinib and showing superiority of erlotinib is missing. Moreover, recent published phase II studies and case reports evaluating the potential clinical activity of erlotinib in patients with EGFR mutated tumours who experienced PD with gefitinib, failed to show a clinically relevant benefit of erlotinib at least for the majority of the patients treated, probably due to potential acquired cross-over resistance.

In the publication of Rosell et al, it is noteworthy that 20% of erlotinib-treated patients seem to be long-term survivors (alive at 36 months). Overall, within the very responsive subset of patients with activating EGFR mutations, it appears that both clinical characteristics (ECOG performance status <1, female gender, adenocarcinoma, absence of brain metastases) as well as molecular characteristics (exon 19 deletions) are associated with a better prognosis (long-term survival).

However, the lack of CSR in the Spanish Lung cancer Group study, was considered a major deficiency from a regulatory perspective. The MAH has been requested to provide more reassurance regarding the data quality and reliability of the SLCG study. The MAH provided additional information about the SLCG study including a protocol outline, list of sites and investigators, CRF, ICF and supplementary tables to the NEJM publication. The choice of treatment was made at each respective institution according to local recommendations. Inclusion criteria were patients with advanced NSCLC (non-squamous). Patients could previously have been treated with chemotherapy so there was no limitation to 1st line treatment in the advanced setting. Patients to whom erlotinib was administered as a 1st line therapy were part of the TARGET clinical substudy. For this subgroup of patients, erlotinib was apparently used in accordance with the Spanish Ministry of Health recommendations on the utilization of drugs for compassionate use. However, no CSR was available for the SLCG study and neither for the TARGET study.

In the analysis of the data provided in the meta-analysis by Paz-Ares et al, and although there appear to be some gaps in the funnel plots, (which could be a chance finding due to the small number of studies or could be indicative of publication bias) the larger studies lie closer to the vertical reference lines (pooled median PFS) in the plots than the smaller studies and these references are in support of an increasing trend in median PFS with chemotherapy-gefitinib-erlotinib. Therefore, even in presence of a publication bias, it appears unlikely that it would affect the conclusion of increasing median PFS with erlotinib compared to chemotherapy or gefitinib. This is also supported by the forest plots. Due to the lack of CSRs from individual studies, this publication could only be considered supportive to the findings of the EURTAC trial.

The SATURN study formed the basis of the approval of erlotinib as maintenance therapy in patients with SD after 4 cycles of platinum-based chemotherapy. Although, the benefit was much larger in patients with activating EGFR mutations, this subgroup was limited and the Risk/Benefit -balance was also considered to be positive in patients with EGFR WT tumours why the indication was not restricted to patients with EGFR activating mutations.

The results of the OPTIMAL study showed a statistically significant superiority for erlotinib versus chemotherapy in terms of PFS in the Asian population. The quality of these data cannot be assessed and the MAH has informed the CHMP that no CSR could be made available. In absence of a CSR, the study results cannot be discussed.

In summary, the interim results from the EURTAC study were considered pivotesl whereas published results without CSRs were only considered supportive in this application.

Methodology for EGFR mutation testing

Only limited information is available regarding the methodologies used to assess the EGFR mutation status in the publications included in this submission. In particular, the CALGB30406 study abstract does not provide any information, and in the pooled analysis publication by Paz-Ares et al. the only comments regarding EGFR mutation testing state that a variety of techniques were used and these were not critically assessed as part of the analysis. The report by Laskin specifies that the EGFR gene status was assessed by DNA sequencing, but no details on how this was performed are provided. On the contrary the publication by Rosell et al. provides a detailed description of the analysis (a laboratory developed method (PB SOP) that was used. It was based on length analysis of the fluorescently labelled PCR product for exon 19 deletions, and a TaqMan assay for the L858R mutations in exon 21. All positive samples were confirmed by DNA sequencing. Prior to DNA extraction, samples were enriched for tumour content by laser-capture micro-dissection. The same methodology is being used in the ongoing EURTAC study.

Finally, in the SATURN study, EGFR mutation analyses were performed using DNA lysates from macro- or micro-dissected tissue samples with a minimum tumour cell content of 60 - 80%. Exons 18–21 of the EGFR gene were amplified by polymerase chain reaction (PCR), and multiple independent products were analysed by Sanger sequencing. Mutations had to be confirmed on both strands of at least two PCR products. Samples were classified EGFR MUT+ if the most commonly observed activating mutations, i.e. deletions in exon 19, and/or the L858R point mutation in exon 21 were detected.

Although tumours with EGFR activation mutations can often be found in NSCLC patients with certain characteristics, patients can not be selected for 1st line TKI therapy based on clinical characteristics only as no characteristics have been identified that are sufficient or necessary for such mutations to occur. Therefore, patient selection must be based on mutational status why the quality and sensitivity of the used EGFR mutation assays becomes essential. Earlier, direct sequencing was commonly used for the detection of EGFR mutations. However, as this method only allows detection of mutant sequences constituting more than 30% of the total genetic content, various alternative detection methods have been taken into use that allow detection in samples containing few tumour cells, e.g. pleural fluid (these include micro-dissection followed by PCR-mediated amplification etc.).

The MAH has adequately discussed the EGFR mutation testing techniques currently in use, the only commercially available kit (TheraScreen EGFR 29 by DxS Ltd) and the tests used in the studies included in this dossier and in ongoing studies. More sensitive tests are under development, and EGFR mutation assays will improve further in the years to come, but overall, it is reassuring that mutational status has been determined according to accepted methodologies by experienced staff at central laboratories.

In addition, the MAH has compared the 3 methodologies in question (sequencing, PB SOP and DxS) and documented that 1) concordance between sequencing and PB SOP was 100% when sequencing samples were enriched for tumour content and 2) 100% concordance was observed between PB SOP and DxS.

The MAH has proposed to include the following text in section 4.4 of the SmPC which is considered acceptable by the CHMP:

"Assessment of EGFR mutation status: When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations".

3.3.2. Clinical safety

- *Evaluation of Safety Parameters*

The safety analysis of study ML20650 (EURTAC) is based on the safety analysis population (SAP). Adverse events were collected up until 28 days after the final administration of study medication but it is important to note that, due to the nature of the treatments the duration of therapy differed in the 2 arms. Chemotherapy was administered to patients for a maximum of 4 cycles (approximately 3 months) whereas erlotinib was administered until PD or unacceptable toxicity (with the median time to PFS being 9.4 months). This may result in a higher incidence of adverse events in the erlotinib arm.

In the TARGET study adverse events (AEs) were reported every 3-4 weeks from baseline until PD or death. AEs (excluding death) that appeared up to 30 days after the last dose of study drug or 30 days after patient withdrawal (whichever was later) were evaluated. Preferred terms were assigned by the sponsor to the original terms entered on the CRF, using MedDRA v8.1.

In study BO18192, following completion of 4 cycles of chemotherapy, AEs were recorded at the baseline visit and then throughout the erlotinib treatment period until PD or withdrawal of the patient. All AEs (related and unrelated) occurring within 28 days of last study medication intake were recorded. Preferred terms were assigned by the sponsor to the original terms entered on the CRF, using MedDRA v11.0.

In the ongoing trial ML20981, AEs were recorded every 3 weeks throughout the trial until PD or death. All deaths occurring during the trial period or within 30 days after completion of the trial are reported. Preferred terms were assigned by the sponsor to the original terms entered on the CRF, using MedDRA v10.

- *Safety Populations*

In the EURTAC study 5 of the 154 randomized patients were excluded from the safety analysis populations (SAP); 3 patients in the chemotherapy arm had no treatment and 2 patients in the erlotinib arm (one patient had no treatment and one patient had no safety follow-up).

The safety analysis populations for the TARGET and BO18192 studies comprised all patients who had received at least one dose of study medication and had at least one safety follow-up, whether withdrawn prematurely or not. Of the 43 patients enrolled in the TARGET study, 42 were included in the safety analysis population.

Of the 49 NSCLC patients with EGFR mutated tumours in study BO18192, 48 patients (26 placebo, 22 erlotinib) were included in the safety analysis population. One patient was excluded from the safety analysis due to unblinding of the study drug as placebo and intake of erlotinib.

In study ML20981, the safety analysis population included all patients who were randomized and received at least one dose of treatment drug. The safety analysis population comprised 155 patients (83 in the erlotinib arm, 72 in the chemotherapy arm).

- *Patient exposure*

Detailed information over extent of exposure and incidence of dose reductions specifically experienced by patients with EGFR activating mutations have been provided only for EURTAC, TARGET, OPTIMAL, and SATURN studies.

In the EURTAC study, the median dose intensity of erlotinib was 150 mg (range 78 mg to 150 mg). Overall, 28% of patients had a dose modification (reduction or interruption). The majority of patients (80%) had no dose reduction. However, 15/75 (20%) patients had their erlotinib dose reduced to 100 mg and 4/75 (5%) patients had their erlotinib dose reduced to 50 mg. The majority of patients (87%) had no dose interruption but 5/75 (7%) had a dose interruption for < 1 week and 8/75 (11%) patients had their dose disrupted for ≥ 1 week.

Overall, the exposure to erlotinib or to the 4 possible chemotherapy regimens, respectively, was considered adequate and representative to allow further evaluation of the safety profile.

Table 22 Summary of Adverse Events, Withdrawals and Deaths by Trial Treatment (SAP)

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

	CHEMOTHERAPY N = 74 No. (%)	ERLOTINIB N = 75 No. (%)
Total Pts with at Least one AE	73 (98.6)	72 (96.0)
Total Number of AEs	527	681
Deaths #	5 (6.8)	10 (13.3)
Study withdrawals due to an AE #	11 (14.9)	9 (12.0)
Patients with at least one		
AE leading to Death	4 (5.4)	7 (9.3)
Serious AE	19 (25.7)	20 (26.7)
Related serious AE	12 (16.2)	5 (6.7)
AE leading to withdrawal from treatment	13 (17.6)	10 (13.3)
AE leading to dose modification/interruption	39 (52.7)	20 (26.7)
Related AE	70 (94.6)	69 (92.0)
Related AE leading to withdrawal from treatment	11 (14.9)	5 (6.7)
Severe AE	49 (66.2)	31 (41.3)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.
Deaths occurred during treatment phase are counted.
Cut-off for statistical analysis: 02AUG2010
AE24 03FEB2011:20:58:34

Note added by PDRD: "Study withdrawals due to an AE" are reported on the "end of treatment" page of the CRF whereas "AEs leading to withdrawal from treatment" are reported on the "AE pages" of the CRF.

In the TARGET study of the 42 patients evaluable for safety, 13 (31%) had a temporary interruption of study treatment, 12 patients (28.6%) had an erlotinib dose reduction to 100 mg/day and in 1 of these 12 patients erlotinib was further reduced to 50 mg/day.
In the OPTIMAL study dose reductions were reported in 5 patients in the erlotinib arm (6.0%) and 28 patients in the chemotherapy arm (38.9%).
In SATURN study of the 48 evaluable patients with EGFR mutated tumours dose reductions were performed in 4 patients treated with erlotinib (2 due to rash) and in 1 patient receiving placebo.

- *Adverse events, Serious Adverse Events and Deaths per study*

EURTAC study

Common AEs

Almost all patients in both treatment arms experienced AEs. The safety profiles of erlotinib compared to standard chemotherapy regimens are quiet distinct. The most common and characteristic AEs associated with erlotinib were diarrhea and rash as expected.

Table 28 Summary of Adverse Events with an Incidence Rate of Least 10%

ae1310
Protocol(s): ML20650 (W20650C)
Analysis: SAFETY ANALYSIS POPULATION Center: ALL CENTERS

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

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010
AE13 03FEB2011:20:57:10

Severity

Seven (7) subjects experienced grade 5 events in the erlotinib arm vs. 4 in the chemotherapy arm. The relatively high number in the erlotinib arm can be explained by the longer treatment duration. Overall, more patients in the chemotherapy arm experienced severe events (grade ≥ 3): 49 patients (66.2%) compared to 31 patients (41.3%) in the erlotinib arm. Common severe events in the chemotherapy arms were neutropenia and asthenia. Common severe events in the erlotinib arm were infections/infestations.

Table 29 Summary of Patients with NCI-CTC Grade 1 – 5 Adverse Events

	Chemotherapy (N = 74)	Erlotinib (N = 75)
Total patients with at least 1 AE	73 (98.6%)	72 (96.0%)
No of patients with at least 1 Grade 1 AE	61 (82.4%)	67 (89.3%)
No of patients with at least 1 Grade 2 AE	61 (82.4%)	55 (73.3%)
No of patients with at least 1 Grade 3 AE	48 (64.9%)	29 (38.7%)
No of patients with at least 1 Grade 4 AE	12 (16.2%)	5 (6.7%)
No of patients with at least 1 Grade 5 AE	4 (5.4%)	7 (9.3%)

Source ae15, page 378

Deaths

At the time of the interim analysis, 28/77 (36%) of patients in the chemotherapy arm vs. 27/77 (35%) of patients in the erlotinib arm (35%) had died, mainly due to progressive disease (PD).

During the active treatment phase, 7% of patients in the chemotherapy arm and 13% of patients in the erlotinib arm died. Of note, the treatment duration was much longer in the erlotinib arm. In the erlotinib arm, 3 deaths were due to PD. Seven (7) deaths were due to SAEs but only one of these deaths was considered to be directly related to the treatment (hepatotoxicity).

Table 30 Summary of Deaths (All Patients)

ddl1_a
Protocol(s): ML20650 (W20650C)
Analysis: ALL PATIENTS Center: ALL CENTERS

Cause of Death	CHEMOTHERAPY N = 77[a] No. (%)	ERLOTINIB N = 77 No. (%)
Total No. of Deaths	28 (36)	27 (35)
PROGRESSIVE DISEASE	21 (27)	18 (23)
PNEUMONIA	1 (1)	3 (4)
MYOCARDIAL INFARCTION	1 (1)	1[b] (1)
CARDIAC ARREST	1 (1)	-
CEREBROVASCULAR ACCIDENT	1 (1)	-
DEATH	-	1 (1)
GASTROINTESTINAL HAEMORRHAGE	-	1 (1)
HEPATOTOXICITY	-	1 (1)
MULTI-ORGAN FAILURE	1 (1)	-
PERICARDITIS	1 (1)	-
PULMONARY EMBOLISM	1 (1)	-
SEPSIS	-	1 (1)
UPPER RESPIRATORY TRACT INFECTION	-	1 (1)

Investigator text for Cause of Death encoded using MedDRA version 13.1.
Percentages are based on N.
Cut-off for statistical analysis: 02AUG2010
DD11 03FEB2011:20:59:42
[a]One patient who died due to PD in the chemotherapy arm was excluded from the ITT population. This patient received treatment prior to randomization. 3 patients did not receive treatment and were excluded from the SAP.
[b]This patient died prior to receiving treatment and was excluded from the SAP

SAEs

25.7% of patients in the chemotherapy arm vs. 26.7% in the erlotinib arm experienced SAEs. In the erlotinib arm, only 5 events were considered to be treatment-related (diarrhea, respiratory tract infection, hepatotoxitiy (grade 5), hyperbiliruminaemia, lung disorder).

Discontinuations

The percentages of patients discontinuing due to AEs were largely similar between treatment arms (14.9% vs. 12%). In the erlotinib arm, 4 of the triggering events were considered to

be treatment-related (mucosal inflammation, diarrhea, rash, lung disorder). This is in line with previous observations.

The safety profile analysis did not change in the updated analysis.

TARGET study

Common adverse events

The most commonly reported AEs (with an incidence ≥ 10%) reported in patients in the TARGET study are shown in Table 6. The most common individual events were diarrhoea (28 patients, 66.7%), asthenia (22 patients, 52.4%), rash (19 patients, 45.2%), alopecia (13 patients, 31.0%), dyspnoea (13 patients, 31.0%) and conjunctivitis (13 patients, 31.0%).

Table 6. Summary of Common Adverse Events (≥ 10% Incidence) in NSCLC Patients with EGFR Mutated Tumours in the TARGET Study

AE SOC Preferred Term	Erlotinib N = 42 n (%)
ALL BODY SYSTEMS	
Total Pts with at Least one AE	42 (100.0)
Total Number of AEs	654
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Total Pts with at Least one AE	36 (85.7)
Rash	19 (45.2)
Alopecia	13 (31.0)
Dry Skin	9 (21.4)
Pruritus	8 (19.0)
Skin toxicity	7 (16.7)
GASTROINTESTINAL DISORDERS	
Total Pts with at Least one AE	33 (78.6)
Diarrhoea	28 (66.7)
Vomiting	11 (26.2)
Constipation	7 (16.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total Pts with at Least one AE	25 (59.5)
Cough	10 (23.8)
Dyspnoea	13 (31.0)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	30 (71.4)
Total Pts with at Least one AE	22 (52.4)
Asthenia	12 (28.6)
Mucosal inflammation	5 (11.9)
Chest pain	5 (11.9)
Pyrexia	
INFECTIONS AND INFESTATIONS	
Total Pts with at Least one AE	26 (61.9)
Folliculitis	12 (28.6)
Respiratory tract infection	6 (14.3)
EYE DISORDERS	
Total Pts with at Least one AE	15 (35.7)
Conjunctivitis	13 (31.0)
NERVOUS SYSTEM DISORDERS	
Total Pts with at Least one AE	13 (31.0)
Dizziness	5 (11.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total Pts with at Least one AE	17 (40.5)
Back pain	6 (14.3)
METABOLISM AND NUTRITION DISORDERS	
Total Pts with at Least one AE	10 (23.8)
Anorexia	8 (19.0)
INVESTIGATIONS	
Total Pts with at Least one AE	7 (16.7)
PSYCHIATRIC DISORDERS	
Total Pts with at Least one AE	8 (19.0)
RENAL AND URINARY DISORDERS	
Total Pts with at Least one AE	5 (11.9)

Severity of adverse events

Most AEs reported in the TARGET study were mild or moderate (NCI-CTC Grade 1 or 2) in intensity. Nineteen patients experienced 49 ≥ Grade 3 AEs. Two patients experienced a Grade ≥ 3 rash and three experienced ≥ Grade 3 diarrhoea. Other Grade ≥ 3 events reported in more than one patient included asthenia (3 patients), dyspnoea (3 patients), folliculitis (2 patients), pneumonia (2 patients), and back pain (2 patients).

Deaths

Thirty-one of the 42 patients (73.8%) in the TARGET study safety population had died at the time of the database cut-off for the safety analysis (April 22, 2010). All but three of the patients died as a result of PD. Of the three patients who died for reasons other than PD, one died as a result of a urinary tract infection and one as a result of antiphospholipid syndrome. Both events were considered unrelated to trial treatment by the investigator. One additional patient died as a result of encephalitis which the investigator reported as being possibly related to trial treatment.

Serious Adverse Events (SAEs)

Fifteen patients in the subpopulation of patients with tumours with activating EGFR mutations from the TARGET study experienced at least one SAE during the treatment period. Most SAEs were reported by no more than one patient each. The only events reported by more than 1 patient were dyspnoea (3 patients), infection (2 patients) and pneumonia (2 patients).

Three patients (7.1%) experienced a SAE considered by the investigator to be related to trial treatment. One patient experienced serious encephalitis, one patient experienced a serious infection and the third patient experienced 2 serious events which were reported as infection and pneumonia.

Adverse Events Leading to Discontinuation / Interruption / Modification of Treatment
One patient receiving erlotinib treatment in the TARGET study was withdrawn from trial treatment as a result of an adverse event. This patient was withdrawn as a result of a Grade 4 skin toxicity which the investigator considered probably related to trial treatment. Note: at the time of the safety analysis for the SLCG study, which included the data from TARGET, no patient had withdrawn as a result of an adverse event.

Skin and Subcutaneous Tissue Disorders
In the TARGET study, skin and subcutaneous tissue disorders as a class were reported in 36 (85.7%) patients. Rash (preferred term, all grades) was the most frequently reported individual event, occurring in 19 patients (45.2%). The majority of these events were grade 1 or 2 in intensity and most patients (34/42; 81.0%) experienced a skin or subcutaneous tissue disorder which was considered related to trial treatment by the investigator. Two patients reported a Grade ≥ 3 rash. Other frequently reported skin and subcutaneous events reported in patients in the TARGET trial included alopecia (13 patients; 31%), dry skin (9 patients; 21.4%), pruritus (8 patients; 19.0%), skin toxicity (7 patients; 16.7%), and erythema (4 patients; 9.5%). The Grade ≥ 3 events acne, nail bed inflammation and onycholysis were each reported by one patient in this organ system. None of the skin and subcutaneous tissue disorders in the TARGET study were reported as SAEs.

SATURN Study (BO18192)

Common adverse events
The most commonly reported AEs reported in the subpopulation of patients with EGFR mutated tumours in study BO18192 are shown in Table 7. A higher percentage of erlotinib EGFR mutation positive patients experienced at least 1 AE (20 patients, 90.9% on erlotinib, compared with the placebo group (12 patients, 46.2%). The most common events in the erlotinib group were rash (erlotinib group 10 patients, 45.5%; placebo group 1 patient, 3.8%), diarrhoea (erlotinib group 8 patients, 36.4%; placebo group 3 patients, 11.5%), cough (erlotinib group 5 patients, 22.7%; placebo group 1 patient, 3.8%), nausea (erlotinib group 4 patients, 18.2%; placebo group 3 patients, 11.5%), dyspnoea (erlotinib group 4 patients, 18.2%; placebo group 1 patients, 3.8%), and headache (erlotinib group 4 patients, 18.2%; placebo group 1 patients, 3.8%).

Table 7. Summary of Common Adverse Events (≥ 10% Incidence in any Erlotinib Treatment Arm) in NSCLC Patients with EGFR Mutated Tumours in Trial BO18192*

AE SOC Preferred Term	Placebo N = 26 n (%)	Erlotinib N = 22 n (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	12 (46.2)	20 (90.9)
Total Number of AEs	43	141
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts with at Least one AE	4 (15.4)	18 (81.8)
Rash	1 (3.8)	10 (45.5)
Pruritus	2 (7.7)	3 (13.6)
Acne	-	3 (13.6)
Dermatitis Acneiform	-	3 (13.6)
Dry Skin	-	3 (13.6)
Skin Fissures	-	3 (13.6)

GASTROINTESTINAL DISORDERS		
Total Pts with at Least one AE	7 (26.9)	12 (54.5)
Diarrhoea	3 (11.5)	8 (36.4)
Nausea	3 (11.5)	4 (18.2)
Vomiting	2 (7.7)	3 (13.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts with at Least one AE	4 (15.4)	9 (40.9)
Cough	1 (3.8)	5 (22.7)
Dyspnoea	1 (3.8)	4 (18.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (23.1)	5 (22.7)
Total Pts with at Least one AE	2 (7.7)	3 (13.6)
Fatigue		
INFECTIONS AND INFESTATIONS		
Total Pts with at Least one AE	1 (3.8)	9 (40.9)
Paronychia	-	3 (13.6)
NERVOUS SYSTEM DISORDERS		
Total Pts with at Least one AE	3 (11.5)	5 (22.7)
Headache	1 (3.8)	4 (18.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts with at Least one AE	3 (11.5)	4 (18.2)
METABOLISM AND NUTRITION DISORDERS		
Total Pts with at Least one AE	1 (3.8)	4 (18.2)
Anorexia	-	3 (13.6)
INVESTIGATIONS		
Total Pts with at Least one AE	-	4 (18.2)
PSYCHIATRIC DISORDERS		
Total Pts with at Least one AE	-	4 (18.2)

* First line maintenance therapy in patients not progressing following completion of 4 cycles of platinum-based chemotherapy

Treatment-related adverse events

In the subpopulation of NSCLC patients with EGFR mutated tumours in study BO18192, 19 of the 22 patients in the erlotinib arm (86.4%) compared with 5 patients (19.2%) in the placebo group experienced AEs considered by the investigator to be related to study treatment. In the erlotinib group, the most common AEs regarded as related were rash (erlotinib 10 patients, 45.5%; placebo 1 patient, 3.8%) and diarrhoea (erlotinib 6 patients, 27.3%; placebo 3 patients, 11.5%). Other AEs in the erlotinib group regarded as related in at least 10% of patients included pruritus (13.6%, placebo 7.7%), acne (13.6%, placebo 0%), dermatitis acneiform, (13.6%; placebo 0%), dry skin (13.6%; placebo 0%), skin fissures (13.6%; placebo 0%), and anorexia (13.6%; placebo 0%).

Severity of adverse events

In the subpopulation of NSCLC patients with EGFR mutated tumours from study BO18192, the majority of AEs were mild or moderate (NCI-CTC Grade 1 or 2). No grade 4 or 5 AEs were reported in the EGFR mutation positive patients. Six patients in the erlotinib group experienced 12 Grade 3 AEs compared with one patient in the placebo group who experienced 1 Grade 3 event. In the erlotinib treatment group, only one patient experienced a Grade 3 rash and one experienced Grade 3 diarrhoea, compared with none in the placebo group. No individual Grade 3 event was reported in more than one patient.

Deaths

In study BO18192, in the subpopulation of patients with EGFR mutated tumours, at the time of the clinical cut-off for the survival analysis, 8 patients in the erlotinib treatment group and 13 patients in the placebo group had died during the treatment period. All 21 patients had died as a result of progressive disease.

Serious Adverse Events

One patient in the subpopulation of NSCLC patients with EGFR mutated tumours in study BO18192 experienced a serious adverse event during the treatment period. This patient, who was receiving erlotinib experienced left ventricular dysfunction. The event was considered unrelated to trial treatment and resolved following corrective treatment.

Adverse Events Leading to Discontinuation / Interruption / Modification of Treatment

None of the patients in the subpopulation with EGFR mutated tumours in study BO18192 were withdrawn from the erlotinib/placebo single agent treatment period as a result of an adverse event. Four patients in the erlotinib subgroup required dose adjustment following AEs compared with 1 patient in the placebo subgroup.

Skin and Subcutaneous Tissue Disorders

Prior to unblinding of study BO18192, the sponsor defined a term "rash" that encompassed all the appropriate MedDRA preferred terms that could be ascribed to rash-related terms. This was done to avoid underestimating the effect of erlotinib on skin disorders by diluting the incidence across multiple preferred terms. An overview of the MedDRA preferred terms which were included in the composite "rash" term is shown in Table 8.

Table 8 Summary of Rash (Composite Term) in Study BO18192

Medical Concept/ Adverse Event	PLACEBO N = 26 No. (%)	ERLOTINIB N = 22 No. (%)
RASH		
Total Pts With at Least one AE	1 (3.8)	17 (77.3)
RASH	1 (3.8)	10 (45.5)
ACNE	-	3 (13.6)
DERMATITIS ACNEIFORM	-	3 (13.6)
SKIN FISSURES	-	3 (13.6)
DERMATITIS	-	1 (4.5)
Total Number of AEs	1	20

Spanish Lung Cancer Group (SLCG) data (Rosell et al., N Engl J Med (2009), 361:958-67.)

Safety data from the SLCG screening feasibility trial were described in the publication by Rosell et al, 2009. The most common AEs were skin rash, reported in 151 patients (69.6%) and diarrhoea reported in 95 patients (43.8%). The majority of AEs were grade 1 or grade 2 in severity. Grade 3 skin toxicity was recorded in 16 patients (7.4%) and grade 3 diarrhoea reported in 8 patients (3.7%). At the time of the analysis for the publication, no patients had been withdrawn as a result of an adverse event. One subject was diagnosed with interstitial lung disease (ILD) 1 month after initiation of treatment with erlotinib. Erlotinib treatment was temporarily interrupted and the event resolved following corticosteroid therapy.

Pooled Analysis of Published Clinical Trial Data (Paz-Ares et al., J. Cell. Moll. Med. Vol 14, N01-2, 2010 pp. 51-69)

No safety information was available for this study.

CALGB30406 Phase II study (Janne et al., J Clin Oncol 28:7s, 2010)

Safety data from the CALGB30406 trial were reported for all patients irrespective of EGFR mutation status. Of the 82 patients receiving erlotinib single agent therapy, 32 patients were identified with EGFR mutations while of the 100 patients receiving erlotinib plus chemotherapy, 35 patients were identified with EGFR mutations.

Grade 3 or 4 toxicities were the only safety data reported in the CALGB30406 study comparing first-line erlotinib therapy alone or in combination with carboplatin/paclitaxel chemotherapy in patients with NSCLC . In the erlotinib arm, grade 3 or 4 hematologic toxicities were reported by 1 and 0 patients, respectively (1% of patients overall). In the erlotinib plus chemotherapy arm, Grade 3 or 4 hematologic toxicities were reported in 28 and 20 patients, respectively (28% of patients overall).
Grade 3 or 4 non-hematologic toxicities were reported by 17 and 2 patients, respectively, treated with single agent erlotinib (17% overall). In the erlotinib plus chemotherapy arm, Grade 3 or 4 non-hematologic toxicities were reported in 39 and 11 patients, respectively (50% overall).

Phase II study (Laskin et al. 2009)
No safety information was available for this study.

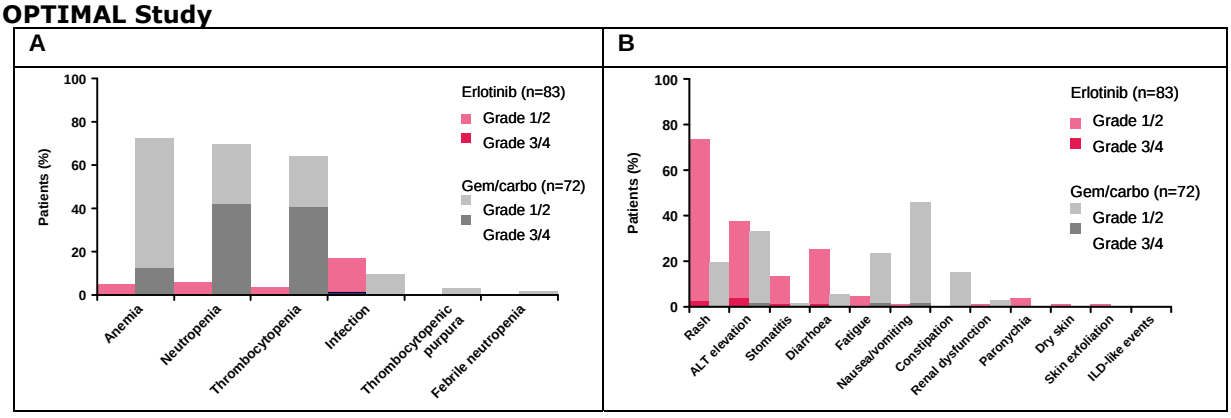
OPTIMAL Study (ML20981)
The safety data confirm the favourable safety profile of erlotinib, with a lower incidence of adverse events and serious adverse events vs. carb/gem. A summary of safety data is provided in table 9. No unexpected adverse events or interstitial lung disease-like events were reported in either arm.

Table 9. Summary of Safety Data in the OPTIMAL Study

	Erlotinib (n=83), %	Carb/Gem (n=72), %
Any AEs (all grades)	92.8	95.8
Treatment-related AEs (all grades)	86.7	94.4
Grade 3 / 4 AEs	16.9	65.3
Dose reduction due to AE	6.0	52.8
Dose reduction due to drug-related AE	6.0	52.8
Discontinuation due to AEs	1.2	5.6
Discontinuation due to drug-related AE	0	5.6
Any serious AEs (SAEs)	12.0	13.9
Treatment-related SAEs	2.4	13.9
Treatment-related death	0	0
Interstitial lung disease (ILD)-like events	0	0

An overview of treatment-related hematologic and non hematologic toxicities is provided in Figure 11.

Figure 11. Treatment-Related Hematologic (A) and Non Hematologic (B) Toxicity in the OPTIMAL Study



At the time of the data cut-off for the safety analysis of OPTIMAL study, a total of 72 patients (86.7%) in the erlotinib treatment arm and 69 patients (95.8%) in the chemotherapy treatment arm had reported at least one adverse event of any grade. The most common all grade AEs (≥ 10% incidence) in patients receiving erlotinib were skin rash (56 patients, 67.5%), ALT increased (25 patients, 30.1%) and diarrhoea (20 patients, 24.1%). In patients in the chemotherapy arm, the most common AEs were thrombocytopenia (46 patients, 63.9%), neutropenia (49 patients, 68.1%), anaemia (52 patients,

72.2%), fatigue (15 patients, 20.8%), skin rash (14 patients, 19.4%) and ALT increased (24 patients, 33.3%). Most patients experienced at least one AE considered by the investigator to be related to study treatment (66 patients, 79.5% in the erlotinib treatment arm and 68 patients, 94.4% in the chemotherapy arm).

Grade ≥ 3 AEs were experienced by 13 patients (15.7%) in the erlotinib treatment arm and 45 patients (62.5%) in the chemotherapy arm, the most common event in the chemotherapy arm being neutropenia (29 patients, 40.3%) and thrombocytopenia (28 patients, 38.9%). The only Grade ≥ 3 AE reported by more than one patient each in the erlotinib treatment arm was ALT increased (3 patients; 3.6%).

Ten patients in each treatment arm experienced a serious adverse event during study treatment. In 2 erlotinib treated patients and all 10 chemotherapy-treated patients, the serious adverse event was considered related to treatment by the investigator.

Dose reduction was reported for 5 patients in the erlotinib arm (6.0%) and 28 patients in the chemotherapy arm (38.9%). In the eroltinib arm, 4 patients had a dose reduction due to elevated ALT levels and one patient had a dose reduction due to stomatitis.

- *Laboratory findings*

In the TARGET, BO18192 and ML20981 studies, standard haematology, biochemistry and urinalysis tests were performed. All safety laboratory assessments were performed locally. Although abnormal laboratory test parameter data were recorded, separate analyses of these data for patients with EGFR mutated tumours were not available from the studies included in this submission.

- *Safety in special populations*

No new information is available.

- *Safety related to drug-drug interactions and other interactions*

No new information is available.

- *Discontinuation / interruption / dose reductions due to AES*

Dose reductions/interruptions for AEs were permitted to take place at any time during each of the TARGET and BO18192 studies. In the event of a dose-limiting toxicity that was not controlled by optimal supportive care, or not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity, the daily dose of erlotinib was to be decreased initially by 50 mg/day. Within 2 weeks following a dose reduction, the erlotinib related toxicity had to improve by at least one NCI-CTC grade and be NCI-CTC Grade < 2, or further dose reduction by 50 mg/day was required. Dosing was permitted to be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity was not controlled by optimal supportive medication.

In particular, erlotinib dosage modification for drug-related diarrhoea and rash was permitted. Once a patient had a dose reduction for toxicity, the dose was not re-escalated, except in the case of erlotinib-related rash. In TARGET and study BO18192, in the event of rash, the dose could be re-escalated when the rash was Grade ≤ 2.

In study ML20981, dose adjustments were to be considered in the event of grade 3-4 rash or diarrhoea not controlled by the active internal medicine, or for other grade 3-4 AEs. For skin rash or diarrhoea, re-medication was considered after recovery to grade 1 or less and with the dose of erlotinib reduced by 50 mg/day. For other AEs after temporary interruption of treatment, re-medication was considered

with a dose reduction of 50 mg after the recovery of the toxicity. In the event of a suspected ILD, erlotinib was to be stopped immediately and only re-started if a diagnosis of ILD was not confirmed.

- *Post marketing experience*

Post marketing data are of minor relevance for the current application as they are not linked to the underlying mutational status.

Discussion on clinical safety

Safety data have been reported in the Spanish study by Rosell et al. As expected, the most common AEs were skin rash, reported in 69.6% of patients and diarrhoea reported in 43.8% of patients. The majority of AEs were grade 1 or grade 2 in severity. Grade 3 skin toxicity was recorded in 16 patients (7.4%) and grade 3 diarrhoea reported in 8 patients (3.7%). Unfortunately, the safety analysis was performed for all patients irrespective of line of therapy why it is of limited value in the evaluation of the safety of erlotinib as first line therapy in NSCLC patients with tumours bearing EGFR mutations. No safety data was available from the pooled study by Paz-Arez et al.

Further evidence comes from the prospectively conducted pivotal EURTAC study that included 75 erlotinib-treated patients in the safety analysis population. In this study, almost all patients treated experienced AEs. Common AEs associated with erlotinib were diarrhoea, rash, infections (paronychia and folliculitis), cough and dyspnea. More patients in the chemotherapy arm experienced severe events grade ≥ 3) (66.2%) than in the erlotinib arm (41.3%). The most common severe events in the erlotinib arm were infections followed by gastrointestinal disorders and general disorders like asthenia.

The frequency of SAEs was similar between treatment arms (25.7% of patients in the chemotherapy arm vs. 26.7% in the erlotinib arm) but their nature differed. In the erlotinib arm, only 5 events were considered to be treatment-related (diarrhea, respiratory tract infection, hepatotoxitiy (grade 5), hyperbiliruminaemia, lung disorder).

The overall safety profile of erlotinib given as 1st line therapy in NSCLC patients with EGFR mutated tumours is considered consistent with the known safety profile of erlotinib described in later lines of therapy where only a minority of patients happened to harbour EGFR mutations. The most commonly reported AEs in the 1st line setting in patients with activating mutations were rash and diarrhoea and the safety profile was overall manageable, although serious or severe events did occur, demanding dose reductions or interruptions. The discontinuation rate was low. No new safety signals have been identified. Similarly, EGFR mutation status has not been found to correlate with the frequency or severity of AEs during gefitinib treatment. There is no indication of a different safety profile of erlotinib in Caucasians compared to Asians why safety results from studies of Asian origin could be extrapolated to European populations. The MAH has not investigated whether a reduced erlotinib dose could actually "suffice" in the treatment of patients with EGFR activating mutations, but the proposed dosage is well-characterized, and the safety profile is considered acceptable although adverse events of erlotinib are not negligible.

Pharmacovigilance system
N/A

Risk Management Plan
The MAH submitted a revised version of the risk management plan (version 3.1) which is considered adequate by the CHMP. The experience with Tarceva in both clinical trials and in the post-marketing setting is large and most side effects have been detected by now.
The safety specification is adequate, and a new identified risk has been added to the list of risks associated with Tarceva use. A drug-drug interaction with statins is a newly identified risk of Tarceva. This new risk is proposed to be handled by routine pharmacovigilance, and depending on the data the need for risk minimisation measures will be evaluated. The rest of the pharmacovigilance plan is adequate.

Regarding risk minimisation, the MAH has generally proposed to use the product information. This is endorsed; therefore the RMP is relevant and adequate to cover the extension of indication. No further actions are warranted at this time.

Table xx Summary of the EU Risk Management Plan

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
Identified Risks		
Cutaneous toxicity	Routine pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see section 4.8). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. SmPC Section 4.8. Undesirable effects: Common: Alopecia, dry skin, paronychia and skin fissures Uncommon: Hirsutism, eyebrow changes, brittle and loose nails and mild skin reactions such as hyperpigmentation Very rare: Stevens-Johnson syndrome/Toxic epidermal necrolysis. Educational materials: Educational materials for prescribers and/or patients to anticipate and manage erlotinib-induced rash. These materials are provided to reassure and guide patients on common adverse events experienced, and not to technically prevent these risks from occurring.
ILD	Routine pharmacovigilance Guided questionnaire	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Cases of ILD have been reported. Confounding factors (prior chemotherapy and radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, pulmonary infections) were frequent. If ILD is diagnosed, Tarceva treatment should be discontinued. SmPC Section 4.8. Undesirable effects: Uncommon: Serious interstitial lung disease. Educational materials: Additional educational materials for prescribers to anticipate and manage ILD. These materials are provided to reassure and guide patients on adverse events experienced, and not to technically prevent these risks from occurring.

Liver Injury	Routine pharmacovigilance Guided questionnaire	Routine risk minimisation by means of labelling SmPC Section 4.4: Special warnings and precautions for use. Rare cases of hepatic failure (including fatalities) have been reported during use of Tarceva. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered. Tarceva dosing should be interrupted if changes in liver function are severe (see section 4.8). Tarceva is not recommended for use in patients with severe hepatic dysfunction. SmPC Section 4.8. Undesirable effects: Very common : Liver function abnormalities Rare: hepatic failure
GI fluid loss	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: In the event of severe or persistent diarrhoea, nausea, anorexia or vomiting associated with dehydration, Tarceva therapy should be interrupted and appropriate measures taken to treat the dehydration. SmPC Section 4.8. Undesirable effects: Table1 and Table 2: diarrhoea, nausea, vomiting, abdominal pain, dyspepsia, flatulence. Educational materials: Additional educational materials for prescribers to anticipate and manage erlotinib-induced diarrhoea. These materials are provided to reassure and guide patients on common adverse events experienced, and not to technically prevent these risks from occurring.
GI Perforation	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly(including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation SmPC Section 4.8. Undesirable effects: Uncommon: Gastrointestinal perforations.

Ocular toxicities	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.4. Special warnings and precautions for use: Very rare cases of corneal perforation or ulceration have been reported during use of Tarceva. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with Tarceva treatment which are also risk factors for corneal perforation/ulceration. Tarceva therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain. SmPC Section 4.8. Undesirable effects : Eye disorders: Common: Keratitis and conjunctivitis Uncommon: Eyelash changes Very rare: Corneal ulcerations and perforations.
Interaction with coumarin anticoagulants	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with coumarin-derived anticoagulants including warfarin leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving Tarceva. Patients taking coumarin derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.
Interaction with statins	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. The combination of Tarceva and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.
Interaction with ketoconazole	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with other medicinal products: caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.
Interaction with ciprofloxacin	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.5. Interaction with other medicinal products.: Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced.
Potential Risks		
Thrombotic Microangiopathy	Routine pharmacovigilance Guided questionnaire	Risk minimization measures not proposed
Missing Information		

Pregnancy and lactating	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.6. Pregnancy and lactation. SmPC Section 5.3. Preclinical safety data.
Paediatrics	Routine Pharmacovigilance	Routine risk minimisation by means of labelling SmPC Section 4.2 Posology and method of administration.
Cardiac disorders	Routine Pharmacovigilance	Risk minimization measures not proposed

3. 4. Anti- EGFR Class labelling requested by the PhVWP/CHMP

The Pharmacovigilance Working Party was requested by CHMP to consider whether a review of reports of keratitis and ulcerative keratitis should be undertaken, with a view to possible harmonisation of the PI for the EGFR inhibitor class of products.

A review of reports of ocular toxicity associated with other EGFR inhibitors on the EudraVigilance database has revealed that cases of keratitis and ulcerative keratitis have been reported in association with the use of all marketed EGFR inhibitors. Consideration should therefore be given to harmonisation of the PI for the EGFR inhibitor class of products.

The PhVWP considered the number of reports of keratitis and ulcerative keratitis across the EGFR class and agreed that warnings about keratitis and ulcerative keratitis should be updated across the class as follows:

'Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with TRADENAME should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Tarceva should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.'

This information was reflected in the SmPC section 4.4 and in the Package Leaflet sections 2 and 4.

4. Benefit risk assessment

Benefits

The EURTAC study is the first prospectively conducted, relatively large randomized, unblinded phase III trial comparing the efficacy of erlotinib to a standard platinum-based doublet regimen in the 1st line treatment of patients with EGFR activating mutations in Europe.

Following review of the interim analysis results of the EURTAC study, the IDMC recommended stopping of the trial after demonstration of a substantial benefit of erlotinib over chemotherapy. At the time the HR for PFS was 0.42 (95% CI 0.27-0.64, p<0.0001) which corresponds to a 58 % reduction in the risk of progression or death. The Kaplan- Meier curves make a clear and early separation. The median PFS for patients in the chemotherapy arm was 5.2 months vs. 9.7 months in the erlotinib arm resulting in an absolute gain of 4.5 months in median PFS in erlotinib-treated patients. This is considered a highly

clinically relevant gain in PFS. The robustness of the result was confirmed in a number of sensitivity analyses, sufficient reassurance has been provided regarding the independent review process and consistent results were found in subgroups with an acceptable sample size.
Results from supportive trials and published literature confirm the findings of the EURTAC study.

Uncertainty in the knowledge about the beneficial effects

N/A.

Unfavourable effects
In conclusion, the overall safety profile of erlotinib given as 1st line therapy in NSCLC patients with EGFR mutated tumours is considered consistent with the known safety profile of erlotinib described in later lines of therapy where only a minority of patients happened to harbour EGFR mutations. The most commonly reported AEs in the 1st line setting in patients with activating mutations were rash and diarrhoea and the safety profile was overall manageable, although serious or severe events did occur, demanding dose reductions or interruptions. The discontinuation rate was low. No new safety signals have been identified.

Benefit-risk balance
The benefit of erlotinib in terms of PFS compared to standard chemotherapy regimens as first line therapy of patients with activating EGFR mutations is considered to be clinically relevant and well documented.
The safety profile of erlotinib is considered acceptable, well-characterized and distinct from the well-known safety profile of standard chemotherapies. The oral administration of erlotinib provides convenience to the patient.

Conclusion
Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/000618/II/0020 for extending the indication of Tarceva (erlotinib) for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations, is approvable.

5. Conclusion

On 21 July 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.