Report according to § 42b (2) German Drug Law

Protocol-No.:	BO18602
Study Title:	A multicenter, open-label, randomized, phase III study to evaluate the efficacy of Tarceva® or comparator Alimta® (pemetrexed) or Taxotere® (docetaxel) in patients with histologically documented, advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (stage IV) non-small cell lung cancer who have experienced disease progression during platinum-based chemotherapy.
Date of Report:	December 2010
Study Sponsor(s)	F. Hoffmann-La Roche Inc.
Study Dates:	10.04.2006 – 01.08.2010
Trial Phase:	III
Indication:	Non-small cell lung cancer
Duration of Treatment:	The recruitment will take place over approximately 45 months (April 2006 to December 2009). The last patient randomized will be followed up for at least 6 months prior to study analysis
Number of Patients:	
Planned	400 patients
Analyzed	424 patients
Study Interruptions/ Premature end:	n/a
Publication (Reference):	Dr Tudor Ciuleanu MD, Lilia Stelmakh MD, Prof Saulius Cicenas MD, Skaidrius Miliauskas MD, Prof Alexandru Calin Grigorescu SR, Carina Hillenbach MSc and others; Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study; Lancet Oncol 2012; 13: 300–08

GLOSSARY OF ABBREVIATIONS

AAG	α-1-Acid glycoprotein
AE	Adverse event
AUC	Area under the plasma concentration-time curve
CA-SSR	CA single sequence repeat
CL/F	Apparent clearance
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FACT-L	Functional Assessment of Cancer Therapy (for Lung Cancer)
FISH	Fluorescence in situ hybridization
HER	Human epidermal (growth factor) receptor
IHC	Immunohistochemistry
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NSCLC	Non small cell lung carcinoma
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial response
QoL	Quality of Life
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
V/F	Apparent volume of distribution

COMPANY: F. Hoffmann-La Roche NAME OF FINISHED PRODUCT: Tarceva® NAME OF ACTIVE SUBSTANCE(S): N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride	

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	BO18602: A multicenter, open-label, randomized, phase III study to evaluate the efficacy of Tarceva® or comparator Alimta® (pemetrexed) or Taxotere® (docetaxel) in patients with histologically documented, advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (stage IV) non-small cell lung cancer who have experienced disease progression during platinum-based chemotherapy. Report Number 1028298. December, 2010		
INVESTIGATORS / CENTERS AND COUNTRIES	77 centers in 24 countries		
PERIOD OF TRIAL	April 10, 2006 – August 1, 2010 (first patient randomized – clinical cut-off date)	CLINICAL PHASE	III
OBJECTIVES	**Primary objective**: to determine if the administration of erlotinib after disease progression whilst receiving a standard platinum-based chemotherapy regimen for the treatment of NSCLC results in improved survival when compared to pemetrexed or docetaxel. **Secondary Objectives**: 1. To compare OS between the treatment arms in patients with: • EGFR protein expression (IHC) positive • EGFR protein expression (IHC) negative 2. To compare PFS between the treatment arms for all patients and in patients with: • EGFR protein expression (IHC) positive • EGFR protein expression (IHC) negative 3. To compare the response rate between the treatment arms 4. To perform exploratory evaluations of available tumor-tissue for biological or genomic determinants of outcome, including but not limited to *EGFR* and *K-ras* mutational status and EGFR and HER2 expression status and other downstream targets.		

	5. To compare time to symptom progression between the treatment arms (Functional Assessment of Cancer Therapy - [FACT-L]). 6. To evaluate the safety profile of administering erlotinib after disease progression with a standard platinum-based chemotherapy in the treatment of NSCLC when compared with pemetrexed and docetaxel. 7. To investigate by a population analysis approach the pharmacokinetics (PK) of erlotinib in the target population, including the influence of covariates and to provide posthoc estimates of exposure. Exploration of the relationship between exposure to erlotinib and safety and efficacy parameters will be performed.
STUDY DESIGN	Multicenter, open-label, randomized, phase III study. The study consisted of 2 components: 1) the screening phase 2) the open-label, randomized, phase III study following a standard (non-investigational) platinum-based chemotherapy. After experiencing disease progression during a standard platinum-based chemotherapy regimen, eligible patients were randomized to either erlotinib (150 mg per day) or comparator (pemetrexed or docetaxel). All treatments continued until disease progression, unacceptable toxicity or death.
NUMBER OF SUBJECTS	2590 patients were screened ; 424 patients randomized (221 comparator arm and 203 erlotinib arm)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	**Before Platinum-Based Chemotherapy (At Screening)** • Patients with histologically documented, locally advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC. • Patients must have measurable disease according to the RECIST criteria. • Previous adjuvant or neo-adjuvant treatment was permitted if completed ≥ 6 months before start of chemotherapy. • ECOG performance status of 0 – 1 **After Platinum-Based Chemotherapy (At Baseline)** • Failure (disease progression) during 1 to 4 cycles of an acceptable, standard, platinum based chemotherapy doublet. (**This was a mandatory requirement for study entry**.) • Patients should have recovered from any toxic effects of platinum-based chemotherapy treatment • ECOG performance status of 0 - 2. • Patients must be able to take oral medication. • At least 4 weeks must have elapsed since any prior surgery or radiotherapy. Patients who, in the opinion of the investigator, have fully recovered from surgery in less than 4 weeks could also be considered for the study.

TRIAL DRUG / STROKE (BATCH) No.	Erlotinib: P425801; T150CB1; X200871; T150CB1; B0002; B0004; B1003; B1010; B1004; X200861; X200661; D6A985
DOSE / ROUTE / REGIMEN / DURATION	150 mg/day oral erlotinib
REFERENCE DRUG / STROKE (BATCH) No.	Available within report
DOSE / ROUTE / REGIMEN / DURATION	• pemetrexed 500 mg/m^2 every 3 weeks • docetaxel 75 mg/m^2 every 3 weeks
CRITERIA FOR EVALUATION	
EFFICACY:	Overall survival, progression-free survival, objective response (RECIST), time to symptom progression (QoL)
PHARMACOKINETICS/ PHARMACODYNAMICS:	CL/F (apparent clearance), V/F (apparent volume of distribution) were estimated using an existing population pharmacokinetic model. The influence of covariates e.g. total bilirubin, alpha 1 acid glycoprotein, gender, albumin levels and smoking status on CL/F was confirmed. An exploratory PK/PD analysis was performed to the relationship of measures of exposure to erlotinib ($AUC_{0-\tau}$) and drug-related AEs such as rash and diarrhoea. The relationship between exposure and clinical efficacy was also explored.
QUALITY of LIFE	The Functional Assessment of Cancer Therapy – Lung (FACT-L). version 4 was used to assess QoL (Physical Well-being, Emotional Well-being, Social Well-Being, and Functional Well-being as well as symptoms commonly reported by lung cancer patients (eg, shortness of breath, loss of weight, tightness in chest).
SAFETY:	Adverse events NCI CTC, version 3, serious adverse events, laboratory parameters, 12-lead ECG.
STATISTICAL METHODS	2-sided non-stratified Log-Rank test for equality of survival at the 5% significance level, median and 95% confidence limits were estimated using Kaplan-Meier survival methodology, hazard ratio was estimated using Cox regression analyses (adjusted and non-adjusted) applying Wald test; response rates were compared using Chi-squared test with 95% confidence limits according to Pearson-Clopper. In addition, 95% confidence limits for the difference using the Anderson-Hauck approach were calculated.

METHODOLOGY:

Eligible patients had experienced progression of their disease whilst receiving (up to 4 cycles of) a standard platinum-based chemotherapy combination. Patients were randomized to either erlotinib or comparator (choice of comparator chemotherapy as most appropriate for the patient was left to the medical judgment of the investigator in countries where both treatments are registered for second line use and are commercially available, otherwise docetaxel was administered). Following randomization, erlotinib (once a day, as a 150 mg tablet) or comparator treatment (administered according to the locally approved label) continued until disease progression, unacceptable toxicity or death. During the investigational phase of the study, all patients receiving either erlotinib or comparator chemotherapy were seen every 3 weeks for assessments of performance status, FACT-L and AEs, as well as administration of comparator chemotherapy. All patients entering the study had 5 PK samples taken, a total of approximately 15 mL blood. A predose blood sample (3 mL) for α-1-acid glycoprotein (AAG) analysis was also taken at each PK sampling day, before erlotinib dosing (a total of 9 mL blood).Once patients had completed 48 weeks of erlotinib/comparator without unacceptable toxicity, patients underwent scheduled clinical assessments every 12 weeks. Patients who progressed had a final visit, after which they were followed for survival every 12 weeks.

EFFICACY RESULTS:

There was no significant difference in OS between the two treatment arms (point estimate in favor of erlotinib). This analysis is supported by stratified, subgroup, sensitivity and robustness analyses based on stratification factors (disease stage, ECOG performance status at baseline, region and smoking status), demographic factors (age, race, sex, histology of NSCLC), previous treatment for NSCLC (previous radiotherapy, previous surgery) and biomarkers (EGFR-IHC, *EGFR*-FISH, *EGFR* mutation status, *K-ras* mutation status, *EGFR CA-SSR1*). Only *K-ras* mutated and *K-ras* wild-type patients showed a difference in treatment effect. For patients with *K-ras* wild-type, the risk of death was lower in the erlotinib arm than in the comparator arm. For the small subgroup of patients with the *K-ras* mutation, the risk of death was lower in the comparator arm than in the erlotinib arm. It is, however, of note that there were imbalances in baseline characteristics between the treatment arms in this small patient subgroup.

There was no statistically significant difference in PFS between the 2 treatment groups although there was a trend towards improved PFS in the comparator arm. Analysis of PFS in the various subgroups supports these data.

The proportion of patients that responded to treatment was low but comparable in each of the treatment arms. However, a higher proportion of patients treated with chemotherapy achieved stable disease compared to patients treated with erlotinib and conversely, a higher proportion of patients treated with erlotinib had PR and PD as their best overall response compared to patients receiving systemic therapy.

PHARMACODYNAMIC RESULTS/ PHARMACOKINETIC RESULTS:

The population PK data obtained in this study were in line with those reported previously in patients with Stage IIIB/IV NSCLC. No obvious relationship between measures of exposure and either efficacy or safety parameters could be identified.

SAFETY RESULTS:

Overall, there were no unexpected safety findings in this study and the safety profile of erlotinib was favorable. Despite having a poor prognosis, the patients randomized to receive erlotinib tolerated the treatment well.

In summary:

- fewer AEs were reported in the erlotinib arm compared to comparator arm (462 vs 575)
- a higher proportion of patients experienced AEs in the erlotinib arm (73.5% vs 70.4%)
- the majority of AEs in both treatment arms were NCI-CTC grade 1 or grade 2 (82% in the comparator arm versus 86% in the erlotinib arm)
- more patients in the erlotinib arm (58.2%) experienced AEs (mainly rash) that were assessed as related to treatment compared to the comparator arm (40.1%)
- fewer deaths due to AEs were reported in the erlotinib arm (2%) compared to the comparator arm (5%)
- fewer patients experienced SAEs in the erlotinib arm (10.2% vs 14.6%)
- fewer patients were withdrawn from treatment due to an AE in the erlotinib arm (2% vs 4.7%)

CONCLUSIONS:

Taking into account the fact that the trial was prematurely halted due to recruitment challenges and hence underpowered, no definitive conclusions can be drawn. However, in this patient population with a poor prognosis:

- There was no significant difference in OS between the two treatment arms (point estimate in favour of erlotinib) in the overall population and in most of the subgroups analyzed.
- There was no significant difference in PFS between the two arms, with a trend towards a better PFS in the comparator arm and this result was consistent in the various subgroups.
- Posthoc analyses indicated that the difference in PFS between treatment arms might in part be due to different censoring patterns and imbalances in the number of patients with rapidly progressive disease.
- The population PK data obtained in this study were in line with those reported previously. No obvious relationship between exposure to erlotinib and either safety or efficacy parameters could be established.
- Safety and tolerance was consistent with the established profile for erlotinib. Erlotinib was better tolerated in this population, compared to chemotherapy, with no hematological toxicities.
- There were fewer deaths due to AEs, SAEs, severe AEs, and withdrawals due to AEs in the erlotinib arm.
- Erlotinib remains an appropriate and tolerable option for patients in the second-line setting who do not derive benefit from first-line platinum chemotherapy, regardless of EGFR (IHC) status.

Efficacy results covering primary objective and secondary objectives no. 1, 2 ,3 and 4

In this patient population with a poor prognosis, the risk of death, and hence the survival, was not statistically different between the treatment arms with the point estimates in favor of erlotinib (HR = 0.96 [95% CI 0.78 to 1.19], p = 0.7299). This result is supported by stratified, subgroup, sensitivity and robustness analyses based on stratification factors (disease stage, ECOG performance status at baseline, region and smoking status), demographic factors (age, race, sex), history of NSCLC and previous treatments related to NSCLC. Median survival was similar in both arms with 5.5 months (95% CI 4.4 to 7.1) in the comparator arm and 5.3 months (95% CI 4.0 to 6.0) in the erlotinib arm. The 1-year estimate of event free rate was 24% in the comparator group compared with 26% in the erlotinib group.

The results from the OS analyses of the various biomarker subgroups (EGFR-IHC, EGFR-FISH, EGFR mutation status, K-ras mutation status, EGFR CA-SSR1 polymorphism), were consistent with that of the overall FAS population; there was no statistically relevant difference in OS between patients treated with comparator and mutation. For patients with K-ras wild-type, the risk of death was lower in the erlotinib arm than in the comparator arm (HR: 0.69; 95% CI 0.49; 0.99). For the small subgroup of patients with the K-ras mutation, the risk of death was lower in the comparator arm than in the erlotinib arm. (HR: 2.2; 95% CI 0.96; 5.06). The small number of patients in this high risk population, combined with a notable imbalance of baseline characteristics (higher proportion of female gender and never smokers in the comparator arm within the K-ras mutated population), prevent any meaningful interpretation of this observation.

Although there was not a statistical difference in PFS between the 2 treatment groups (HR = 1.19; [95% CI 0.97; 1.46] p = 0.0885), there was a trend towards more favorable PFS in the comparator arm. The median time to an event in the comparator arm was 8.6 weeks (95% CI: 7.1;12.1) compared to 6.3 weeks (95% CI: 6.1;6.9) in the erlotinib arm, both close to the time of the first tumor assessment, 6 weeks after commencing therapy. The PFS results in the overall population were supported by a consistent PFS in the various sub-groups including demography, stratification factors, history of NSCLC, previous treatments related to NSCLC as well as biomarkers (EGFR-IHC, EGFR-FISH, EGFR mutation status, K-ras mutation status, EGFR CA-SSR1 polymorphism).

The difference in outcomes of OS and PFS, in addition to the large amount of early censoring for PFS, prompted exploratory analyses of both PFS and OS. While no imbalances in censoring patterns in OS were seen, these further analyses indicated that for PFS, the difference between the treatment arms might in part be due to confounding factors, mainly due to different censoring patterns and imbalances in the number of patients with a tendency to quickly progress and who thus received the trial treatment for only a short duration.

Overall, the proportion of patients that responded to treatment was low but similar in both the treatment arms. However, a higher proportion of patients treated with chemotherapy achieved stable disease compared to patients treated with erlotinib and conversely, a higher proportion of patients treated with erlotinib had partial response as their best overall response compared to patients receiving chemotherapy. Limited patient numbers for analysis, combined with high censoring rates, limit the validity of the QoL results. However, there was no statistically significant difference in any QoL measurements, but ,as with PFS, there was a trend favoring the comparator arm.

Tabular Summary of Overall Efficacy Results

Parameter	Comparator Arm	Erlotinib Arm
Overall Survival (OS)		
median (months)	5.5	5.3
HR (95% CI); p-value* (Log-Rank test)	0.96 (0.78;1.19), p = 0.7299	
OS in EGFR (IHC)-positive subgroup		
median (months)	5.5	5.6
HR (95% CI) p-value (Log-Rank test)	0.94 (0.72; 1.21); p = 0.6198	
OS in EGFR (IHC)-negative subgroup		
median (months)	6.7	5.4
HR (95% CI) p-value (Log-Rank test)	0.95 (0.55;1.62), p = 0.8398	
OS in *EGFR* Activating Mutation		
median (months)	-	19.3
HR (95% CI) p-value (Log-Rank test)	1.19 [0.12;11.49], p = 0.8820	
OS in *EGFR* Wild-type		
median (months)	4.4	6.6
HR (95% CI) p-value (Log-Rank test)	0.85 (0.59; 1.22), p = 0.3725	
Progression-Free Survival (PFS)		
median (weeks)	8.6	6.3
HR (95% CI); p-value (Log-Rank test)	1.19 (0.97; 1.46), p = 0.0885	
PFS in EGFR (IHC)-positive subgroup		
median (weeks)	8.9	6.3
HR (95% CI); p-value (Log-Rank test)	1.26 (0.98; 1.61), p = 0.0662	
PFS in EGFR (IHC)-negative subgroup		
median (weeks)	11.5	6.7
HR (95% CI); p-value (Log-Rank test)	1.02 (0.61; 1.69), p = 0.9403	
PFS *EGFR*-Activating Mutation		
median (weeks)	43.0	36.3
HR (95% CI); p-value (Log-Rank test)	0.71 (0.13; 3.97), p = 0.6965	
PFS in *EGFR* Wild-type		
median (weeks)	8.9	6.3
HR (95% CI); p-value (Log-Rank test)	1.25 (0.88; 1.78), p = 0.2030	
Best Overall Response		
responders	6.3%	7.9%
non-responders	93.1%	92.1%
p-value (Chi-squared test)	0.5349	

*p-values are on non-stratified analysis

Results of secondary objective no.5: Time to Symptom Progression (QoL)

At the baseline visit, FACT-L completion rates were around 90% and remained above 80% in both treatment arms as the study progressed.

Only 165 (75%) patients in the comparator arm and 158 (78%) patients in the erlotinib arm were available for analysis of time to symptomatic progression and nearly 40% of the available patients were censored for this analysis, limiting the value of the analysis of QoL. In general, QoL is closely linked to disease progression and thus to PFS. Moreover, QoL data were only collected during the treatment period so, progressive disease according to RECIST criteria before worsening of symptoms led to (informative) censoring for the QoL endpoints, further limiting the interpretation of the QoL endpoints. However, from the available data, the time to symptomatic progression was similar in both treatment arms (HR [95% CI] 1.19 [0.90; 1.57], p = 0.2202), see table below.

Protocol(s): BO18602 (V18602G)
Analysis: Full Analysis Set

	COMPARATOR (N=221)		ERLOTINIB (N=203)
Patients included in analysis	165 (100.0 %)		158 (100.0 %)
Patients with event	100 (60.6 %)		98 (62.0 %)
Patients without event*	65 (39.4 %)		60 (38.0 %)
Time to event (weeks)			
Median#	9.0		7.1
95% CI for Median#	[7.0;12.1]		[6.1;9.3]
25% and 75%-ile	4.3;26.7		3.7;30.0
Range##	1.3 to 49.4		2.7 to 114.1
p-Value (Log-Rank Test)		0.2202	
Hazard Ratio		1.19	
95% CI		[0.90;1.57]	
6 months estimate			
Patients remaining at risk	13		17
Event Free Rate#	0.27		0.27
95% CI for Rate#	[0.18;0.36]		[0.18;0.35]

Time to Symptomatic Progression [Weeks] (TTTSP_W) - Censoring: TTSP Censoring (1=event, 0=censored) (CSTTSP)
* censored
# Kaplan-Meier estimates
including censored observations
Cut-off for statistical analysis: 07SEP2010

Program : $PROD/cdl1677d/bo18602/ettsp_t.sas
Output : $PROD/cdl1677v/v18602g/reports/ettsp_t_2000.out
08SEP2010 10:23

Results of secondary objective no. 6: Evaluation of Safety Profile

Summary of Adverse Events of Relevance to the Known Safety Profile of Erlotinib

Body System/ Adverse Event	COMPARATOR	ERLOTINIB
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	37 (17.4)	105 (53.6)
RASH	7 (3.3)	74 (37.8)
ALOPECIA	25 (11.7)	-
DERMATITIS ACNEIFORM	1 (0.5)	12 (6.1)
ACNE	-	11 (5.6)
DRY SKIN	1 (0.5)	8 (4.1)
PRURITUS	1 (0.5)	7 (3.6)
NAIL DISORDER	-	3 (1.5)
RASH PRURITIC	2 (0.9)	1 (0.5)
EXFOLIATIVE RASH	-	2 (1.0)
HYPERHIDROSIS	1 (0.5)	1 (0.5)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	-	2 (1.0)
URTICARIA	1 (0.5)	1 (0.5)
DERMATITIS	-	1 (0.5)
ERYTHEMA	1 (0.5)	-
ONYCHOLYSIS	-	1 (0.5)
PIGMENTATION DISORDER	-	1 (0.5)
RASH MACULAR	-	1 (0.5)
RASH PAPULAR	-	1 (0.5)
SKIN EXFOLIATION	-	1 (0.5)
SKIN TOXICITY	-	1 (0.5)
TOXIC SKIN ERUPTION	-	1 (0.5)
Total Number of AEs	40	130
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	54 (25.4)	56 (28.6)
DIARRHOEA	12 (5.6)	37 (18.9)
NAUSEA	29 (13.6)	15 (7.7)
CONSTIPATION	10 (4.7)	6 (3.1)
VOMITING	8 (3.8)	7 (3.6)
STOMATITIS	8 (3.8)	2 (1.0)
ABDOMINAL PAIN	6 (2.8)	2 (1.0)
ABDOMINAL PAIN UPPER	2 (0.9)	5 (2.6)
ABDOMINAL DISTENSION	2 (0.9)	2 (1.0)
DYSPEPSIA	2 (0.9)	1 (0.5)
DYSPHAGIA	2 (0.9)	1 (0.5)
TOOTHACHE	3 (1.4)	-
DRY MOUTH	2 (0.9)	-
BREATH ODOUR	1 (0.5)	-
COLITIS	1 (0.5)	-
DUODENAL ULCER	1 (0.5)	-
ENTEROCOLITIS	1 (0.5)	-
ENTEROVESICAL FISTULA	-	1 (0.5)
FLATULENCE	-	1 (0.5)
GASTRIC PERFORATION	1 (0.5)	-
GLOSSODYNIA	-	1 (0.5)
MOUTH HAEMORRHAGE	-	1 (0.5)
OESOPHAGITIS	1 (0.5)	-
ORAL PAIN	1 (0.5)	-
PERIANAL ERYTHEMA	1 (0.5)	-
PROCTITIS	-	1 (0.5)
SUBILEUS	-	1 (0.5)
UPPER GASTROINTESTINAL HAEMORRHAGE	1 (0.5)	-
Total Number of AEs	95	84
EYE DISORDERS		
Total Pts With at Least one AE	6 (2.8)	11 (5.6)
CONJUNCTIVITIS	1 (0.5)	3 (1.5)
DRY EYE	-	4 (2.0)
VISION BLURRED	1 (0.5)	2 (1.0)
LACRIMATION INCREASED	2 (0.9)	-
CONJUNCTIVAL HYPERAEMIA	-	1 (0.5)
DIPLOPIA	1 (0.5)	-
EYE PAIN	-	1 (0.5)
KERATOCONJUNCTIVITIS SICCA	-	1 (0.5)
OCULAR HYPERAEMIA	1 (0.5)	-
RETINAL VEIN THROMBOSIS	-	1 (0.5)
Total Number of AEs	6	13

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.

Results of secondary objective no. 7: Population Pharmacokinetic Analysis and the Exploratory PK/PD Analysis:

The objectives of the current PK/PD analysis was to investigate the pharmacokinetics of erlotinib in NSCLC patients and furthermore to explore the potential relationship between exposure to erlotinib and measures of safety and efficacy. The dataset used for this analysis was a subset of the entire dataset for study BO18602. A total of 147 patients out of 203 patients (72%) randomized to erlotinib treatment were included in the dataset.

An existing population-pharmacokinetic model developed from a population of patients comparable to the patient population in study BO18602 could successfully be applied to the data from this study. A similar bias is present in both model population predictions with an underprediction of high concentrations and an overprediction of the low concentrations. This bias is mainly due to noise observed in the collected sparse PK data. Despite this bias, the model adequately described the individual plasma concentrations of erlotinib. The covariates influence on erlotinib clearance (CL/F) identified previously appeared to be appropriate also for the BO18602 dataset. The PK data obtained in this study were in line with those reported previously in patients with Stage IIIB/IV NSCLC and the exposure to erlotinib derived by the Bayesian feedback approach were therefore used to investigate the exposure-safety and exposure-efficacy relationships.

Since previous PK/PD analysis failed to show clear relationships between exposure to erlotinib and efficacy or safety parameters, it was decided to perform the PK/PD analysis for TITAN in two steps. The first step of this analysis focused on the relationship between exposure versus diarrhoea and exposure versus rash as key safety parameters, and on exposure versus OS, exposure versus PFS, and on exposure versus best response as key efficacy parameters. Since the outcomes of those analyses confirmed the lack of any relevant exposure-response relationship, the second step of the PK/PD analysis, which consisted in exploring the potential influence of patient baseline characteristics and covariates on those relationships, was not performed.

For the safety analysis, the influence of the exposure at the time of an event (AUC_{24}) was plotted against grade of rash and diarrhoea. Higher grades of rash seem to be associated with higher exposure to erlotinib. However, at all rash grades 1 - 3, the range of exposure overlaps with the exposure range observed in patients without rash (grade 0) indicating that the observed trend is rather weak.

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

The predictive power of the exposure to erlotinib for progression free survival, overall survival and best response was explored graphically using the mean exposure over the treatment duration. No perceptible relationship between the exposure to erlotinib and efficacy measures could be clearly identified.

Overall, no obvious relationship between exposure to erlotinib and either safety (rash and diarrhoea) or efficacy parameters (PFS, OS and best response) could be established.

Batch-No. for Pemetrexed and Erlotinib

0541038E	D5H424	D7D378
A240497	D5H433	D7D736
A250249	D5H513	D8A421
A255188	D60320	D8C035
A255239	D61285	D8D084
A272337	D64081	D8D124
A274747	D6A046	D90915
A283149	D6A053	D9C643
A294810	D6A065	D9C681
A304253	D6A065/D5H	D9C830
A307206	D6A066	D9C914
A309564	D6A073	D9C924
A334347	D6A204	FF5244AG
A349951	D6A292	FF52936
A352000	D6A331	FF5574E
A380274	D6A334	FF5644AG
A384198	D6A353	FF5974E
A456777F	D6A641	FF5G66Z
A543393C	D6A675	FF5H23AD
A566322	D6A677	FF5L40H
A566322L	D6A685	FF5L44AG
A5728452	D6A882	FF5L44AM
A572845L	D6A976	FF5S20T
A5861784	D6A985	FF5S21D
A586179H	D6C150	FF5S44J
A610479C	D6C153	FF5S74E
A638548N	D6C195	FF5S74J
A638598N	D6C316	FF5V59D
A639696J	D6C433	FF6B55G
B0002	D6C434	FF6C66P
B0004	D6C666	FF6E81M
B1003	D6C673	FF6J68E
B1004	D6C674	FFGE818
B1010	D6C681	I511670
D5E961	D6C975	I537654
D5F027	D6D097	LY8274747
D5F277	D6D318	NK
D5G339	D6D320	O6A898
D5G584 D6A	D6D392	P425801
D5G816	D6E068	T150CB1
D5G904	D6ED319	UNKNOWN
D5G904/D5G	D7A061	X200661
D5H107	D7A278	X200861
D5H121	D7A509	X200871
D5H380	D7A748	
D5H417	D7C519	
D5H417 D5G	D7D376	

Protocol Amendments

Protocol Amendment 1 (Protocol Version B), dated July 28th, 2005.

- Clarification that registered, commercially available pemetrexed was to be administered.
- It was decided that the proposed week 6 extra ECGs were not required, since the week 3 ECGs would provide sufficient information.

Protocol Amendment 2 (Protocol Version C), dated July 23rd, 2007

- The schedule for cisplatin was corrected to every 3 weeks (not 4 weeks).
- Clarification of the RECIST criteria for tumor response evaluation was provided.
- Computed tomography (CT) scan of the pelvis was not mandatory at screening and baseline, provided an abdominal CT scan down to the level of the adrenal glands was performed.

  The protocol was amended to allow tumor assessments within 4 weeks prior to starting the platin-based chemotherapy, and within 4 weeks prior to the first dose of TITAN study drug (erlotinib/comparator chemotherapy). This was to avoid unnecessary restriction for patient enrolment, without compromising the study results.
- The protocol was amended to clarify which patients were to be excluded from the study; patients who have previously received agents directed at the HER axis, agents directed at pemetrexed molecular targets, or prior chemotherapy or therapy with systemic anti-neoplastic therapy (eg, monoclonal antibody therapy or any experimental therapy) for advanced disease other than permitted platinum-based chemotherapies were excluded.
- Dyspnoea was further characterized: severe dyspnoea in relation to acute respiratory distress syndrome.
- Protocol was amended to indicate that patients had to start study drug treatment within 7 days following randomization.
- Recruitment was slower than expected; the number of patients required for screening was increased (from 1700 to 3700) and the length of study was increased (from 3 months long-term follow-up to 18 months long-term follow-up).

Protocol Amendment 3 (Protocol Version D), dated February 3rd, 2010.

- Changes were made to the follow-up measures. Given the difficulties with recruitment, the sample size for the study was revised from the original 631 patients to approximately 400 patients, corresponding to a recruitment end of December 2009, leading to a reduction of power to a maximum of 60%.
- Safety signals were updated in line with core data sheet (version 9) for erlotinib including rash, interstitial lung disease-like events, diarrhoea, dehydration, electrolyte imbalance and renal failure, hepatitis, hepatic failure, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, drug-drug interaction (since erlotinib is metabolized mainly by cytochrome P450 (CYP)3A4 and CYP1A2).

Country	Main Account
GREECE	Univ General Hosp Heraklion; Medical Oncology
DENMARK	ODENSE SYGEHUS; ONKOLOGISK AFDELING
AUSTRIA	PULMONOLOGISCHES ZENTRUM DER STADT WIEN; II. ABT. FÜR INTERNE LUNGENERKRANKUNGEN
FRANCE	GH Paris Saint Joseph; Hopital De Jour Oncologie
AUSTRIA	LHK KLAGENFURT; LUNGENABT.
AUSTRIA	Lkh innsbruck - univ. Klinikum innsbruck - Tiroler landeskrankenanstalten ges.m.b.h.; Innere Medizin
RUSSIAN FEDERATION	N.N. BLOKHIN CANCER RESEARCH CENTER; DEPARTMENT OF CLINICAL PHARMACOLOGY AND CHEMOTHERAPY
RUSSIAN FEDERATION	CLINICAL ONCOLOGY DISPENSARY OF MINISTRY OF HEALTH OF TATARSTAN
CANADA	CANCER CARE MANITOBA
AUSTRALIA	ROYAL NORTH SHORE HOSPITAL; ONCOLOGY
RUSSIAN FEDERATION	CENTRAL RESEARCH INST. OF ROENTGENRADIOLOGY
BELGIUM	A.Z. MIDDELHEIM
RUSSIAN FEDERATION	SAINT-PETERSBURG CITY CLINICAL ONCOLOGY DISPENSARY
RUSSIAN FEDERATION	SI of Healthcare Kazan Oncology Dispensary
RUSSIAN FEDERATION	SI of Healthcare Kazan Oncology Dispensary
CHINA	BEIJING UNION HOSPITAL
GREECE	SOTIRIA HOSPITAL
LITHUANIA	Klaipeda University Hospital
CHILE	CENTRO DE ONCOLOGICOS SANTIAGO
SLOVENIA	INSTITUTE OF ONCOLOGY LJUBLJANA
RUSSIAN FEDERATION	MOSCOW REGIONAL ONCOLOGY HOSPITAL; CHEMOTHERAPY
HUNGARY	UNI OF SZEGED; PULMONOLOGY DEPT
HUNGARY	BARANYA COUNTY HOSPITAL; PULMONOLOGY DEPT
AUSTRALIA	GEELONG HOSPITAL; ANDREW LOVE CANCER CENTRE
SPAIN	HOSPITAL UNIV. CENTRAL DE ASTURIAS; ONCOLOGY
SPAIN	HOSPITAL MARQUES DE VALDECILLA; ONCOLOGY
UNITED KINGDOM	NINEWELLS HOSPITAL; CANCER MEDICINE
KOREA, REPUBLIC OF	SEOUL NATIONAL UNI HOSPITAL; DEPT. OF INTERNAL MEDICINE/HEMATOLOGY/ONCOLOGY

Country	Main Account
AUSTRALIA	AUSTIN AND REPATRIATION MEDICAL CENTRE; CANCER SERVICES
GERMANY	Stiftung Kathol. Krankenhaus Marienhospital Herne Klinik Mitte Medizinische Klinik III
POLAND	MEDICAL ACADEMY OF LODZ; CHEMOTHERAPY
GERMANY	AUGUSTA KRANKENANSTALT; KLINIK FÜR HAEMATOLOGIE/ONKOLOGIE
NEW ZEALAND	AUCKLAND CITY HOSPITAL; ONCOLOGY
NEW ZEALAND	CHRISTCHURCH HOSPITAL; DEPT OF ONCOLOGY
CHINA	SUN YAT-SEN UNI OF MEDICAL SCIENCE; CANCER CENTER
CANADA	ALGOMA REGIONAL CANCER PROGRAM; SAULT AREA HOSPITAL
UNITED KINGDOM	LEICESTER ROYAL INFIRMARY; DEPT. OF MEDICAL ONCOLOGY
UNITED KINGDOM	BROOMFIELD HOSPITAL; ONCOLOGY
HUNGARY	JOSA ANDRAS KORHAZ; DEPT OF ONCORADIOLOGY
KOREA, REPUBLIC OF	SAMSUNG MEDICAL CENTRE; DIVISION OF HEMATOLOGY/ONCOLOGY
DENMARK	Herlev Hospital; Onkologisk afdeling
SLOVAKIA	FAKULTNA NEMOCNICA ROOSEVELTA; DEPT. OF ONCOLOGY
FRANCE	CENTRE OSCAR LAMBRET; UNITE DE RECHERCHE CLINIQUE
SPAIN	Complejo Hospitalario Universitario A Coruña (CHUAC), Oncology
FRANCE	Chu Site Du Bocage;Pneumologie
FRANCE	CENTRE HOSPITALIER DU MANS; MALADIES RESPIRATOIRES
FRANCE	HOPITAL BRABOIS ADULTES; PNEUMOLOGIE
ROMANIA	CLINICAL CITY HOSPITAL TIMISOARA; ONCOLOGY CLINIC
ROMANIA	INSTITUT OF ONCOLOGY CHIRICUTA CLUJ-NAPOCA; ONCOLOGY
ROMANIA	UNI HOSPITAL ST. SPIRIDON; CLINICA ONCOLOGIE-RADIOTHERAPIE
ROMANIA	INSTITUT OF ONCOLOGY AL. TRESTIOREANU BUCHAREST; ONCOLOGY
LITHUANIA	UNI ONCOLOGY INST. ; CHEMO - RADIATION DEPT
AUSTRALIA	NEWCASTLE MATER MISERICORDIAE HOSPITAL; ONCOLOGY
RUSSIAN FEDERATION	MEDICAL ACADEMY OF POSTGRADUATE EDUCATION; CITY CLINICAL HOSPITAL #3
CZECH REPUBLIC	FAKULTNÍ NEMOCNICE OLOMOUC; DEPT OF PNEUMOLOGY
UKRAINE	NATIONAL MEDICAL UNI , FACULTY OF POSTGRADUATE EDUCATION; SURGERY DEPT. ONCOLOGY COURSE

Country	Main Account
UKRAINE	INST. OF MEDICAL RADIOLOGY, AMS OF UKRAINE; ONCOLOGY
GERMANY	Schwarzwald-Baar Klinikum/VS GmbH; Onkologie/Hämatologie/Infektologie
AUSTRALIA	ST VINCENT'S HOSPITAL; MEDICAL ONCOLOGY
ITALY	Ospedale Bellaria; Divisione Oncologia
SLOVAKIA	INST. OF TB & RESPIRATORY DISEASES; DEP. OF ONCOLOGY
SLOVAKIA	NATIONAL INST. OF TB & RESPIRATORY DISEASES; DEP. OF PNEUMO-ONCOLOGY
SLOVAKIA	INST. OF TB & RESPIRATORY DISEASES; CLINICAL ONCOLOGY & PNEUMOLOGY
CZECH REPUBLIC	FAKULTNI NEMOCNICE V PLZNI; PLICNI KLINIKA
RUSSIAN FEDERATION	N.N.BURDENKO MAIN MILITARY CLINICAL HOSPITAL; ONCOLOGY DEPT
KOREA, REPUBLIC OF	ASAN MEDICAL CENTER, UNI ULSAN COLLEGEMEDICINE; DEPT.INTERNAL MEDICINE / DIVISIONHEMATOLOGY/ONCOLOGY
SOUTH AFRICA	MEDICAL ONCOLOGY CENTRE OF ROSEBANK; ONCOLOGY
RUSSIAN FEDERATION	CITY ONCOLOGY HOSPITAL; CHEMOTHERAPY DEPT
UKRAINE	Regional Oncology Center ; Thoracic Oncology
CZECH REPUBLIC	NEMOCNICE CESKE BUDEJOVICE; ODDELENI PLICNI A TBC
FRANCE	HOPITAL DU CLUZEAU; SERVICE DE PATHOLOGIE RESPIRATOIRE
CANADA	LAKERIDGE HEALTH OSHAWA; ONCOLOGY
CANADA	HOPITAL DU SACRE COEUR DE MONTREAL; ONCOLOGY
POLAND	MAZOWIECKIE CENTRUM LECZENIA CHOROB PLUC I GRUZLICY; ODDZIAL III
AUSTRALIA	FLINDERS MEDICAL CENTER; MEDICAL ONCOLOGY
HUNGARY	KORANYI NATIONAL INST. OF TBC & PULMONOLOGY I & XIV; DEPT OF PULMONARY MEDICINE
HUNGARY	KORANYI NATIONAL INST. OF TBC & PULMONOLOGY I & XIV; DEPT OF PULMONARY MEDICINE
HUNGARY	KORANYI NATIONAL INST. OF TBC & PULMONOLOGY I & XIV; DEPT OF PULMONARY MEDICINE
HUNGARY	INST. OF PULMONARY MEDICINE, TOROKBALINT; 2ND DEPT OF PULMONARY MEDICINE
FRANCE	CENTRE ONCOLOGIE DU PAYS BASQUE
RUSSIAN FEDERATION	RUSSIAN RESEARCH CENTER OF ROENTGENORADIOLOGY; DEPT OF CHEMOTHERAPY
RUSSIAN FEDERATION	Regional Clinical Oncology Dispensary
ITALY	UNI CATTOLICA POLICLINICO GEMELLI; ONCOLOGIA MEDICA IST. MEDICINA INTERNA

Country	Main Account
SOUTH AFRICA	LITTLE COMPANY OF MARY HOSPITAL; MARY POTTER ONCOLOGY CENTRE
CANADA	CITE DE LA SANTE DE LAVAL; HEMATO-ONCOLOGIE
SPAIN	HOSPITAL CLÍNICO UNIV. LOZANO BLESA; ONCOLOGY
HUNGARY	SEMMELWEIS UNI , FACULTY OF GENERAL MEDICINE; PULMONOLOGY CLINIC
GERMANY	ZENTRALKLINIK BAD BERKA GMBH; PNEUMOLOGIE
GERMANY	Ruppiner Kliniken Medizinische Klinik A
GERMANY	Krankenhaus Martha-Maria Klinik für Innere Medizin I
RUSSIAN FEDERATION	REGIONAL CLINICAL ONCOLOGY DISPENSARY; SURGERY DEPT, THORACIC
RUSSIAN FEDERATION	REGIONAL CLINICAL ONCOLOGY DISPENSARY; SURGERY DEPT, THORACIC
FRANCE	HOPITAL GABRIEL MONTPIED; SERVICE DE PNEUMOLOGIE
AUSTRALIA	MONASH MEDICAL CENTRE; ONCOLOGY
MALAYSIA	MOUNT MIRIAM HOSPITAL; ONCOLOGY
RUSSIAN FEDERATION	REGIONAL ONCOLOGY CENTRE; ONCOLOGY
RUSSIAN FEDERATION	KIROV STATE MEDICAL ACADEMY; ONCOLOGY
RUSSIAN FEDERATION	KIROV STATE MEDICAL ACADEMY; ONCOLOGY
RUSSIAN FEDERATION	REGIONAL ONCOLOGY DISPENSARY; ONCOLOGY
RUSSIAN FEDERATION	CITY ONCOLOGY DISPENSARY; ONCOLOGY
RUSSIAN FEDERATION	CENTRAL CLINICAL DIAGNOSTIC COMPLEX OF NMSC; ONCOLOGY
ITALY	OSPEDALI RIUNITI DI ANCONA; ONCOLOGY
CHINA	CANCER HOSPITAL, FUDAN UNI ; ONCOLOGY
KOREA, REPUBLIC OF	YONSEI CANCER CENTER; YONSEI UNI COLL. MED.
CHINA	Guangdong General Hospital; ONCOLOGY DEPT
POLAND	MEDICAL UNI OF LODZ; PNEUMOLOGY
HUNGARY	VAS MEGYEI MARKUSOVSZKY KORHAZ; ONCORADIOLOGY
RUSSIAN FEDERATION	PAVLOV STATE MEDICAL UNI ; BONE MARROW TRANSPLANTATION CLINIC
KOREA, REPUBLIC OF	ST VINCENT'S HOSPITAL; ONCOLOGY
LITHUANIA	MEDICAL UNI ; ONCOLOGICAL HOSPITAL
SLOVENIA	UNI CLINIC OF RESP DISEASES; RESPIRATORY

Country	Main Account
SLOVENIA	GENERAL HOSPITAL MARIBOR; RESPIRATORY
RUSSIAN FEDERATION	SI of HealthCare Oncologic Dispensary #2 of department of healthcare of Krasnodar region
VENEZUELA	CLINICA EL AVILA; CENTRO INTEGRAL DE ONCOLOGIA
RUSSIAN FEDERATION	CENTER OF THORAX SURGERY; ONCOLOGY
RUSSIAN FEDERATION	STATE MEDICAL ACADEMY AFTER MECHNIKOV; THORACIC SURGERY
MALAYSIA	UNI MALAYA MEDICAL CENTER; CLINICAL ONCOLOGY UNIT, MENARA TIMUR
FRANCE	Hopital Augustin Morvan; Federation De Cancerologie
FRANCE	CENTRE HOSPITALIER; PNEUMOLOGIE
SOUTH AFRICA	The Oncology Center
CANADA	TORONTO EAST GENERAL HOSPITAL; HAEMATOLOGY/ONCOLOGY
RUSSIAN FEDERATION	ST-PETERSBURG REGIONAL ONCOLOGY DISPENSARY; ONCOLOGY
UNITED KINGDOM	PLYMOUTH ONCOLOGY CENTRE; CLINICAL TRIALS UNIT
KOREA, REPUBLIC OF	KEIMYUNG UNI DONGSAN MEDICAL CENTER; MEDICAL ONCOLOGY
AUSTRIA	SMZ - Baumgartner Hohe, Pavilion Leopold; 1.Interne Lungenabteilung, Onkologische Tagesklinik
KOREA, REPUBLIC OF	KOREAN CANCER CENTER HOSPITAL; ONCOLOGY
RUSSIAN FEDERATION	Regional Clinical Oncology Hospital
FRANCE	HOPITAL LARREY; CLINIQUE DES VOIES RESPIRATOIRES
GREECE	AGIOI ANARGYROI; 3RD DEPT. OF MEDICAL ONCOLOGY
FRANCE	Centre Georges Francois Leclerc; Oncologie 3