SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BO18602)

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	(FOR NATIONAL AUTHORITY USE ONLY)

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 [redacted] December, 2010		
INVESTIGATORS / CENTERS AND COUNTRIES	77 centers in 24 countries Principal Investigator: [redacted] Romania		
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: [redacted]
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.