SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BO21129)

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	A phase II Biomarker Identification Trial for Erlotinib (Tarceva®) in Patients with Advanced Pancreatic Carcinoma / [redacted] /Month Year		
INVESTIGATORS / CENTERS AND COUNTRIES	49 centers in 15 countries: Australia, Brazil, Bulgaria, India, Italy, Lithuania, Malaysia, Romania, Russia, United Kingdom, Latvia, Singapore, China, Slovenia, and Croatia. 50 investigators		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	24-Jun-2008 to 20-Dec-10 (clinical data cut-off date)	CLINICAL PHASE	II
OBJECTIVES	**Primary**: The primary objective of this study was the identification of biomarker(s) which may predict improvement in progression-free survival (PFS) from treatment with erlotinib. **Secondary**: The secondary objectives of this study were to explore safety and efficacy (response rate, disease control rate [DCR], overall survival [OS]) in patients with advanced pancreatic cancer.		
STUDY DESIGN	Multicenter randomized, double blind, placebo-controlled trial. During the screening phase, a screening examination was performed in the 28 days prior to randomization. During the treatment phase, treatment started on day 1 and continued until disease progression, unacceptable toxicity, withdrawal or death. Follow-up occurred until disease progression, intolerable toxicities, withdrawal or death.		
NUMBER OF SUBJECTS	207 randomized: 103 = placebo and 104 = erlotinib		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with histologically or cytologically confirmed locally advanced-unresectable or metastatic pancreatic cancer where tumor is accessible for biopsy. Patients with ECOG PS 0-2 who have failed one prior regimen of standard chemotherapy or who were deemed unsuitable for chemotherapy. Patients must have measurable disease according to RECIST (irradiated lesions cannot be used as target lesions).		
TRIAL DRUG / STROKE (BATCH) No.	Erlotinib ([redacted] and [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	150 mg, once daily (po) until disease progression, unacceptable toxicity, withdrawal or death.		
REFERENCE DRUG / STROKE (BATCH) No.	Placebo ([redacted] and [redacted]		

DOSE / ROUTE / REGIMEN / DURATION	150 mg, once daily (po) until disease progression, unacceptable toxicity, withdrawal or death.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary parameter**: PFS **Secondary parameters**: • Response rate • DCR • OS • CA 19-9
PHARMACOKINETICS:	The trough concentrations of erlotinib (Ctrough) at week 3 and progression or withdrawal are listed with summary statistics.
SAFETY:	Adverse events, serious adverse events, laboratory tests, vital signs, electrocardiogram, and performance status. The intensity of all AEs and laboratory parameters were graded according to the NCI-CTCAE on a 5-point scale (Grade 1 to 5).
STATISTICAL METHODS	The primary efficacy variable is PFS. The evaluation was performed on all randomized patients, as well as for the subsets defined by the following biomarkers: • EGFR immunohistochemistry (IHC) (positive and negative) • *EGFR* fluorescence in situ hybridization (FISH) (positive and negative) • K-*ras* mutation (mutated [classical] and wild type) • *EGFR* mutation (mutated [activating] and wild type) • *EGFR* CA-SSR1 (low and high) All analyses were performed in an exploratory fashion, providing descriptive information on efficacy within biomarker subgroups. Because of the exploratory nature of the analyses, no adjustment of p-values for multiple testing was performed. For each analysis a 2-sided log-rank test provided a basic comparison of the two treatment groups without adjustment for further potential prognostic factors. Median and 95% confidence limits were estimated using Kaplan-Meier survival methodology. Plots of the Kaplan-Meier estimates for each treatment group were also produced. Six-month rates from randomization were compared using estimates from the Kaplan-Meier survival curves. The Cox proportional hazards model was used to estimate the hazard ratio (HR) (erlotinib compared with placebo), including 95% confidence intervals. Forest plots were provided to illustrate the results for the subgroups. After observing imbalances in some baseline characteristics (more patients over 65 years of age, more patients with a weight loss of over 10% within 6 months before randomization, more patients with pancreatic pain, and more patients with poorly differentiated tumor histology) across treatment arms, post-hoc analyses using multivariate Cox-regression were performed in order to correct for these imbalances and to assess their impact on PFS and OS. In total 30 baseline characteristics (instead of 14 that were originally planned) were investigated.

	In the first step, univariate Cox-regression was performed to test each factor separately, and also to test the treatment effect adjusted by 1 factor. The Kendall's tau B coefficient was calculated to check the potential correlation of the baseline characteristics. The final model, resulting from the stepwise selection (at an alpha level of 0.15) in the FAS, was then also applied to the biomarker subgroups and forest plots were produced to illustrate the results.

METHODOLOGY:

At screening, a tumor biopsy obtained before the start of treatment was mandatory (primary tumor or metastasis) to perform biomarker analysis.

Patients were randomly assigned 1:1 to treatment groups using an adaptive randomization method (minimization).

The minimization ensured a balanced stratification by treatment arm for the following factors:

- Smoking status (current* smoker vs. former smoker vs. never smoker).
- Performance status (PS) (0-1 vs. 2).
- Region (Asian** vs. non-Asian).

* Current smoker included patients who had stopped smoking within the past year.

** Region 'Asian' included countries from South-East-Asia, i.e., excluding India.

The study has not ended yet. The trial will end when the last patient stopped treatment with blinded erlotinib or placebo and completed their final visit before withdrawal or the start of the open-label extension phase. The cut-off date for the statistical analysis was 6 months after the last patient was randomized. It was likely that some patients would still be on study treatment at this time. These patients continued to be treated with erlotinib/placebo until disease progression, intolerable toxicities, withdrawal or death.

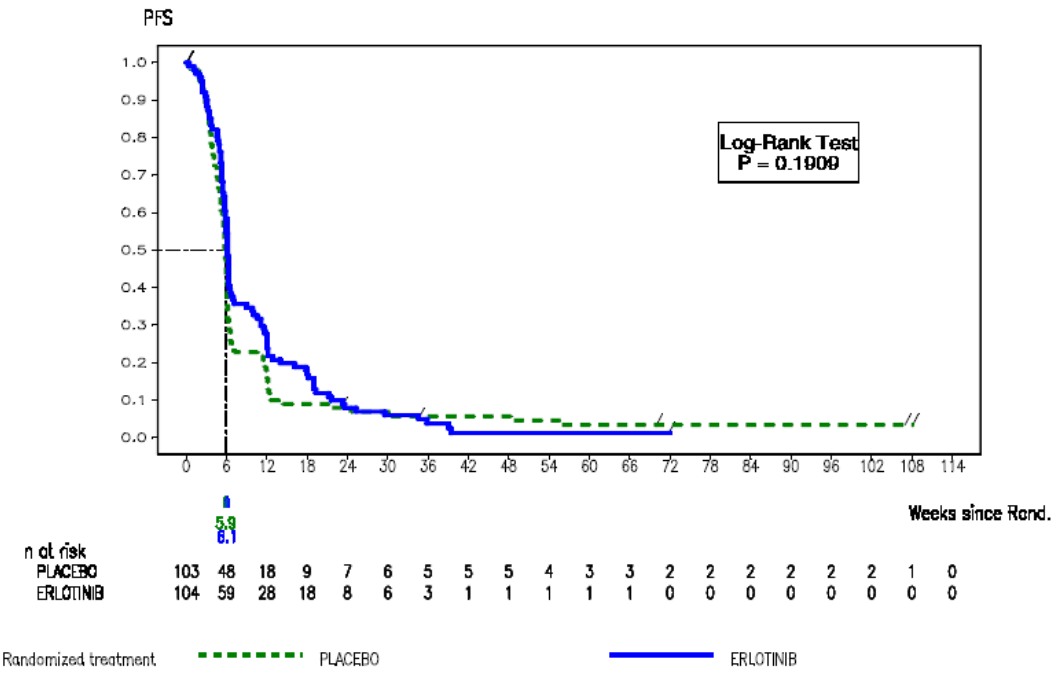
After study un-blinding, when the statistical analyses were performed, the patients still ongoing in the trial were withdrawn from the blinded treatment phase. If it was in the patients' interest, they were allowed to enter the open-label extension phase to receive erlotinib until disease progression, intolerable toxicities, withdrawal or death or switch to commercial supplies.

EFFICACY RESULTS:

No formal testing of hypotheses was performed and therefore no adjustment for multiplicity was performed.

Overall, there was improvement in the primary parameter PFS when comparing the erlotinib arm with the placebo arm, but the difference was not significant in the unstratified, unadjusted analysis (HR = 0.83; 95% CI 0.63-1.10; p = 0.1909 log-rank; 5.9 and 6.1 median number of events in the placebo and erlotinib arms, respectively) (see Figure of Kaplan-Meier Curve of PFS: unadjusted analysis). However, a number of imbalances in baseline characteristics were noted which indicated a worse prognosis in the erlotinib arm, namely more patients over 65 years of age, more patients with a weight loss of over 10% within 6 months before randomization, more patients with pancreatic pain, and more patients with poorly differentiated tumor histology. Post-hoc analyses using multivariate Cox-regression were performed in order to correct for these imbalances and the adjusted analysis for PFS showed a statistically significant effect of erlotinib (HR = 0.68, 95%CI 0.50-0.91, p = 0.0102).

eratepfs_g_2000 Kaplan-Meier Curve of Progression Free Survival
Protocol(s): BO21129 (Y21129B)
Analysis: Full Analysis Set



Cut-off for statistical analysis: 22DEC2010

Program : $PROD/cd11677d/bo21129/eratepfs_g.sas / Output : $PROD/cd11677y/y21129b/reports/eratepfs_g_2000.cgm
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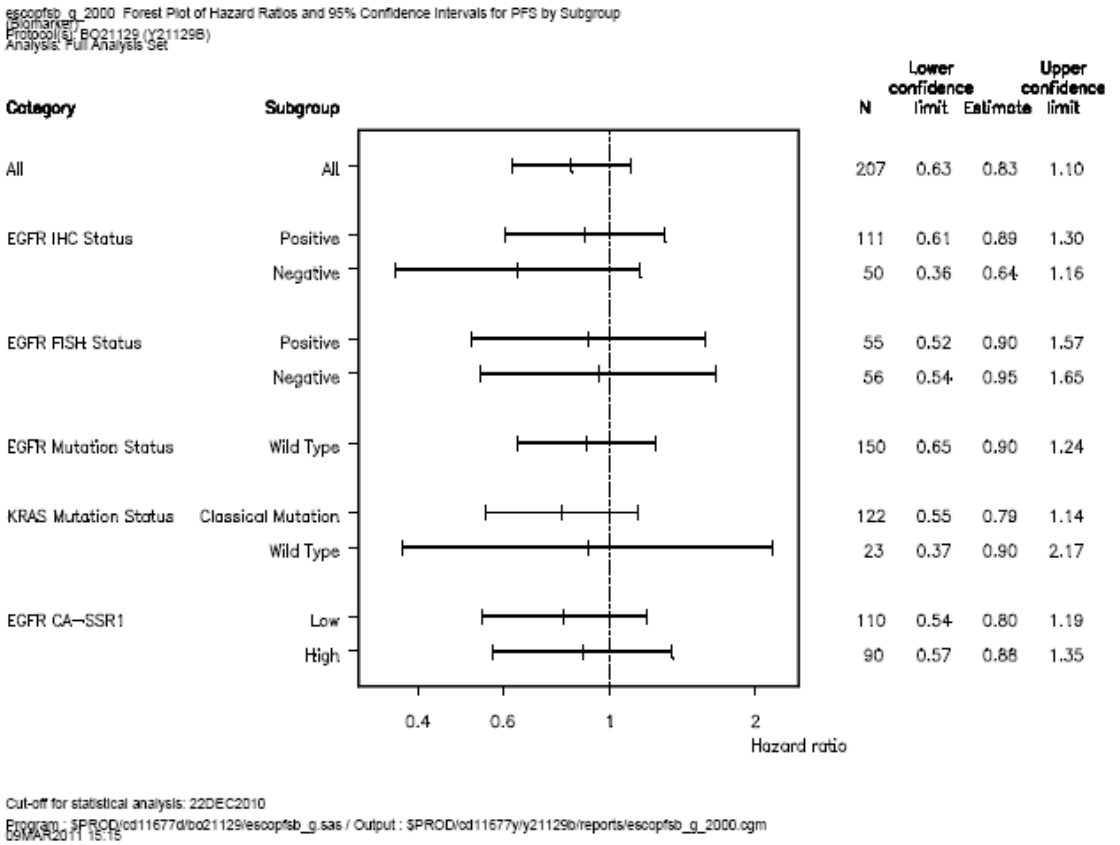
For the primary endpoint of PFS, the biomarker results did not identify a population subset with a detrimental effect or particular benefit after treatment with erlotinib in this population of patients with advanced pancreatic cancer and an extremely poor prognosis (see Figure of Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Subgroup below).



The OS did not differ significantly between the placebo and erlotinib treatment arms in the overall population (HR = 1.04; 95% CI 0.77-1.39; p = 0.8137). This was also confirmed in the multivariate Cox-regression that was performed to correct for the imbalances in some of the baseline characteristics (adjusted OS: HR = 0.83 95%CI 0.60-1.16).

The secondary endpoints of OS, response rate, and DCR did not show any improvement within the various biomarker subgroups.

Overall, the number of responders (confirmed CR or PR) was low (4 PRs in the placebo arm and 1 PR in the erlotinib arm). Therefore the response rates did not allow for sufficient analyses of the biomarker results.

Fewer patients experienced disease control in the placebo arm (18.4%) than in the erlotinib arm (27.9 %). Overall, the DCR (including SD for at least 6 weeks post-randomization) showed improvement by 9.44% in the erlotinib arm compared with the placebo arm (p = 0.1077).

PHARMACOKINETIC RESULTS:

The mean ± SD erlotinib plasma concentration of 1140 ± 914 ng/mL in patients administered erlotinib 150 mg po for 3 weeks was in the range of concentrations observed in patients with locally advanced or metastatic pancreatic cancer, with high variability (mean concentration 1650 ± 922 ng/mL). A similar mean ± SD erlotinib plasma concentration of 1010 ± 910 ng/mL at the time of progression or withdrawal was observed indicating that steady state was achieved within 3 weeks.

SAFETY RESULTS:

Overall, the safety profile of erlotinib in this study was consistent with the profile observed in earlier studies. More patients in the erlotinib arm experienced AEs, AEs related to study treatment, AEs leading to death, SAEs related to study treatment, AEs leading to withdrawal from treatment, related AEs leading to withdrawal from treatment, and AEs leading to dose modification or interruption than those in the placebo arm. The most commonly reported AEs with an incidence of ≥ 10% were rash (46.2% vs. 8.7%), diarrhea (24% vs. 14.6%), nausea (21.2% vs. 7.8%), fatigue (15.4% vs. 8.7%), pyrexia (12.5% vs. 6.8%), asthenia (11.5% vs. 4.9%), decreased appetite (17.3% vs. 10.7%), weight decreased (10.6% vs. 4.9%), and anemia (12.5% vs. 5.8%) in the erlotinib and placebo arms, respectively. In the erlotinib arm, the high frequency of EGFR-associated rash (55 patients [52.9%]) was consistent with the known safety profile of erlotinib. One patient was withdrawn from the study due to grade 3 rash. No patient was withdrawn from the study due to diarrhea.

No AEs of ILD were reported in the erlotinib arm. No unexpected safety findings were observed in an evaluation of laboratory parameters. The majority of patients' worst laboratory parameter values were assessed as ≤ grade 2 in both treatment arms. Overall, the shifts in laboratory parameters were from grade 0 or 1 at baseline to mild or moderate (grade 1 or grade 2) in grade intensity. Some differences were observed between treatment arms in the frequency of patients with grade 3 and grade 4 laboratory abnormalities. More patients experienced shifts in liver enzyme parameters (total bilirubin, GGT, ALT [SPGT], and AST [SGOT]) and lymphopenia to grade 3 or grade 4 in the erlotinib arm than in the placebo arm.

The cumulative dose of study treatment was slightly higher in the erlotinib arm (6525 mg) than in the placebo arm (6300 mg) and a greater proportion of patients received treatment for > 3 months with erlotinib (22%) than with placebo (10%). Erlotinib was well tolerated as demonstrated by the low frequencies of dose reductions (10 patients [10%]) and interruptions longer than 7 days (4 patients [4%]).

One event of death in the erlotinib arm was due to ischemic stroke. According to the investigator, the event was attributed both to the study drug and to the underlying conditions of deep venous thrombosis and pulmonary embolism. Ischemic stroke is not an event in the Tarceva® product label. Roche conducted a Drug Safety Report on September 2010 and concluded that there did not appear to be an increased risk of cerebrovascular ischemia in pancreatic cancer patients treated with erlotinib. One patient in the erlotinib arm, who died of hepatic failure, had metastatic pancreatic cancer and metastatic lesions in the liver at screening. The investigator considered the hepatic failure related to study treatment and considered the underlying liver metastasis as an etiological factor.

An overview of the safety data is summarized in the following table:

ae24_trt Summary of Adverse Events, Withdrawals and Deaths by Trial Treatment
- Blinded Treatment Phase
Protocol(s): BO21129 (Y21129B)
Analysis: SAFETY ANALYSIS POPULATION Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

	PLACEBO	BLINDED ERLOTINIB
	N = 103	N = 104
	No. (%)	No. (%)
Total Pts with at Least one AE	71 (68.9)	90 (86.5)
Total Number of AEs	262	394
Deaths #	35 (34.0)	40 (38.5)
Study withdrawals due to an AE #	2 (1.9)	9 (8.7)
Patients with at least one		
AE leading to Death	2 (1.9)	5 (4.8)
Serious AE	11 (10.7)	21 (20.2)
Related serious AE	2 (1.9)	11 (10.6)
AE leading to withdrawal from treatment	3 (2.9)	10 (9.6)
AE leading to dose modification/interruption	8 (7.8)	16 (15.4)
Related AE	23 (22.3)	69 (66.3)
Related AE leading to withdrawal from treatment	2 (1.9)	8 (7.7)
Severe AE	38 (36.9)	42 (40.4)

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.
Cut-off for statistical analysis: 22DEC2010
AE24 09MAR2011:15:07:24

CONCLUSIONS:

- The biomarker results did not identify a population subset with a particular strong benefit or detrimental effect after treatment with erlotinib in patients with advanced or metastatic pancreatic cancer with a poor prognosis.
- The improvement in unadjusted PFS for erlotinib in the primary analysis of the overall population, although in favor of erlotinib, was not statistically significant (HR = 0.83, 95% CI-0.63-1.10, p = 0.1909). In a post-hoc analysis using multivariate Cox-regression that was performed to correct for the imbalances in some of the baseline characteristics, the adjusted PFS showed a statistically significant effect of erlotinib (HR = 0.68, 95%CI 0.50-0.91, Wald test's p-value = 0.01).
- The secondary endpoints of OS, response rate, and DCR did not show any difference between the 2 treatment arms.
- A total of 57 out of 102 patients (55.9%) in the blinded placebo arm received open-label erlotinib after PD. The OS did not differ significantly between the placebo and erlotinib treatment arms in the overall population (HR = 1.04; 95% CI 0.77-1.39; p = 0.8137). This was also confirmed in the multivariate Cox-regression that was performed to correct for the imbalances in some of the baseline characteristics (adjusted OS: HR = 0.83 95%CI 0.60-1.16, Wald's test p-value = 0.2867).
- Overall, the number of responders (confirmed CR or PR) was low (4 PRs in the placebo arm and 1 PR in the erlotinib arm). Therefore the response rates did not allow for sufficient analyses of the biomarker results.
- Overall, the DCR (including SD for at least 6 weeks post-randomization) showed improvement by 9.44% in the erlotinib arm compared with the placebo arm (p = 0.1077).
- The mean ± SD erlotinib plasma concentration of 1140 ± 914 ng/mL in patients administered erlotinib 150 mg po for 3 weeks was in the range of concentrations observed in patients with locally advanced or metastatic pancreatic cancer, with high variability (mean concentration 1650 ± 922 ng/mL).
- Erlotinib was well tolerated with a safety profile consistent with erlotinib observed in previous single-agent studies. No new safety concerns were identified in patients with advanced or metastatic pancreatic cancer.