SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NO21160B)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, placebo controlled study to determine the effect of two dose schedules of R1507 or placebo, both in combination with erlotinib (Tarceva®), on progression-free survival in patients with advanced non-small cell lung cancer with disease progression after first or second line chemotherapy. Report No. [redacted] May 2011. [redacted]		
INVESTIGATORS / CENTERS AND COUNTRIES	Fifty-one study centers globally, with centers in United States of America, Canada, Australia and Europe.		
PUBLICATION (REFERENCE)	NA		
PERIOD OF TRIAL	5th November 2008 to 14th June 2010	CLINICAL PHASE	II
OBJECTIVES	The primary objective was to define the proportion of patients with progression-free survival (PFS) at 12 weeks with the combination of R1507 and erlotinib or a corresponding placebo and erlotinib, in patients with advanced Stage IIIB/IV NSCLC who had failed at least one, but no more than 2 standard chemotherapy regimens. The secondary objectives were to: • Define the effect of adding R1507 to erlotinib on PFS, overall survival, objective response rate, and duration of response. • Describe the population pharmacokinetic (PK) profile of R1507 when combined with erlotinib. • Evaluate the safety profile of R1507 in combination with erlotinib in patients with advanced NSCLC. • Explore 2 doses and schedules of R1507 combined with erlotinib in this setting. • Explore changes in pharmacodynamic (PD) markers in responders and non-responders. • Explore candidate biomarkers related to drug mechanism of action.		
STUDY DESIGN	This was a placebo-controlled, parallel group, randomized, phase II trial to evaluate 2 dose schedules of R1507 combined with erlotinib compared to erlotinib and placebo. Patients were initially randomized to schedule (weekly [qw] versus every 3 weeks [q3w]) in an open fashion. Patients were		

	subsequently to be randomized to receive R1507 at 9 mg/kg or placebo qw or R1507 at 16 mg/kg or placebo q3w in a blinded fashion. Erlotinib at 150 mg per oral (po) daily starting on study day 1, was to be administered continuously in all cohorts. There were 4 treatment arms. For analysis, patients receiving both qw and q3w placebo were to be combined and evaluated as one group.
NUMBER OF SUBJECTS	A minimum of 129 evaluable patients were to be recruited, 43 for each of the erlotinib plus R1507 arms, and 43 for both erlotinib plus placebo arms combined. To allow for 14% non-evaluable patients, a total of approximately 150 patients was planned. A total of 172 patients were recruited with each participating center recruiting between 1 and 12 patients.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female patients age ≥ 18 years with histologically documented inoperable, locally advanced or metastatic (stage IIIb and stage IV) NSCLC. (Sputum cytology alone was not acceptable). Tumors with mixed histology were to be categorized according to the predominant cell type. Patients had to have failed one, but no more than 2 standard chemotherapy regimens.
TRIAL DRUG / STROKE (BATCH) No.	R1507 (prepared from Chinese hamster ovary [CHO]) was provided in 20 mL single dose vials as a freeze-dried powder; which had to be reconstituted with 4.9 mL of water for injection [redacted] Once reconstituted, the vial contained 125 mg/5 mL of R1507.
DOSE / ROUTE / REGIMEN / DURATION	Patients were to receive their assigned dose of R1507 (9 mg/kg or 16 mg/kg) or placebo as an intravenous (iv) infusion (over 90 minutes for the first infusion, and over 60 minutes for subsequent infusions) qw (for the 9 mg/kg dose), or q3w (for the 16 mg/kg dose) without scheduled interruption. Treatment was to continue until disease progression or as described in the study protocol.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo was normal saline.
DOSE / ROUTE / REGIMEN / DURATION	Administered IV for 90 minutes for the first infusion and for 1 hour for subsequent infusions.
OTHER TRIAL DRUG/BATCH NO.	Erlotinib was supplied as either 25 mg [redacted] or 150 mg [redacted] tablets.
DOSE / ROUTE / REGIMEN / DURATION	Erlotinib was to be administered at a once daily oral dose and continued until disease progression, unacceptable toxicity or the patient's wish to withdraw from the trial. Tablets were to be taken preferably in the morning with up to 200 mL of water one hour before or 2 hours after meals. In case of emesis after taking erlotinib, the patient was not to take another tablet.
CRITERIA FOR EVALUATION	
EFFICACY:	The planned primary endpoint was progression-free survival (PFS) at 12 weeks. PFS was defined as the time from date of first dose of study medication to first date of documented disease progression or death.

SAFETY:	Safety was determined by the reporting of adverse events (AE), the assessment of routine laboratory values (blood counts and differential, serum chemistries, urinalysis), findings on physical examinations, by carefully observing patients for infusion reactions and by determination of human anti-human antibodies (HAHA).
STATISTICAL METHODS	All patients randomized and who had received at least one dose of R1507 or placebo were to be included in the all-treated population. In the all-treated population, patients were to be assigned to treatment groups as randomized for efficacy analysis purposes. Assessment of response was based primarily on investigator assessment in the all-treated population. The safety analysis population included all patients who had received at least one dose/infusion of R1507 or placebo and who had at least one post-baseline safety assessment. Patients were assigned to treatment groups according to the treatment actually received. Adverse event data are presented in frequency tables (overall and by intensity) by body system. In tables showing the overall incidence of AE, patients who experienced the same event on more than one occasion were to be counted only once in the calculation of the event frequency.

METHODOLOGY:

All patients had to have provided written informed consent before any study specific assessments or procedures were performed. A screening examination was to be performed between -28 and 1 days before first day of treatment. Patients who fulfilled the entry criteria were randomized to schedule (qw versus q3w) in an open fashion and subsequently randomized to receive R1507 or placebo. Erlotinib at 150 mg po was administered continuously in all cohorts. Patients had computed tomography/magnetic resonance imaging every 6 weeks. Patients who were progression-free and alive at 12 weeks continued to receive R1507 and erlotinib. Those with progressive disease came off study medication.

REASONS FOR TERMINATION:

[redacted] There were no safety issues involved in the decision to discontinue. Not all efficacy parameters described in the protocol were assessed.

RESULTS:

EFFICACY RESULTS:

The addition of R1507 to erlotinib failed to result in a significant improvement in the 12 week PFS or OS on this unselected population of patients with advanced stage NSCLC who had failed at least one but no more than 2 prior regimens. A potential trend toward moderate improvement in efficacy was demonstrated in the q3w cohort.

Progression-free survival at 12 weeks is summarized in Table 1.

Table 1 Summary of Progression-Free Survival Rate at 12 Weeks by Trial Treatment

t_resp2_A Summary of Progression-Free Survival Rate at 12 Weeks by Trial Treatment
Protocol(s): NO21160
Analysis: ALL TREATED POPULATION

	Placebo (N=57)	9mg/kg QW (N=57)	16mg/kg Q3W (N=57)
Progression-Free & Alive	18 (31.6 %)	16 (28.1 %)	21 (36.8 %)
Progressed, Died, or Unknown	39 (68.4 %)	41 (71.9 %)	36 (63.2 %)
CI for PFS Rate *	[21.5; 43.2]	[18.5; 39.5]	[26.2; 48.6]

* Exact 90% CI by Clopper and Pearson

Table 2 Summary of Adverse Events, Deaths and Withdrawals

ae24 Summary of Adverse Events, Deaths and Withdrawals
Protocol(s): NO21160
Analysis: SAFETY Center: ALL CENTERS
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

	Placebo QW N = 26 No. (%)	Placebo Q3W N = 29 No. (%)	Placebo Total (QW+Q3W) N = 55 No. (%)	R1507 9mg/kg QW N = 59 No. (%)	R1507 16mg/kg Q3W N = 57 No. (%)	R1507 Total (QW+Q3W) N = 116 No. (%)
Total Pts with at Least one AE	26 (100)	27 (93)	53 (96)	57 (97)	56 (98)	113 (97)
Total Number of AEs	172	169	341	471	508	979
Deaths #	20 (77)	22 (76)	42 (76)	43 (73)	34 (60)	77 (66)
Patients with at least one AE leading to Death	1 (4)	0 (0)	1 (2)	3 (5)	5 (9)	8 (7)
Serious AE	5 (19)	3 (10)	8 (15)	18 (31)	14 (25)	32 (28)
AE leading to withdrawal from treatment	2 (8)	0 (0)	2 (4)	7 (12)	10 (18)	17 (15)

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page.

The safety profile was similar to that seen previously with administration of R1507 and with that of monotherapy erlotinib. Although no new safety issues were raised it appears that the addition of R1507 to erlotinib did lead to an increase in AEs typically seen with erlotinib monotherapy, including rash, diarrhea, nausea and fatigue.

CONCLUSIONS:

- The addition of R1507 to erlotinib in an unselected group of patients with advanced NSCLC in the second or third-line setting failed to show significant improvement in efficacy.
- A slight improvement in PFS at 12 weeks was observed in the treatment arm which received R1507 16 mg/kg q3w in combination with erlotinib compared to both the placebo group and the R1507 9 mg/kg qw group.
- Two putative predictive biomarker signals were observed, which potentially can be applied to define a sub-population of patients who may benefit from the investigational regimens, if validated by independent studies.
- The safety profile of R1507 in combination with erlotinib was as expected and no new safety issues were noted.
- A higher incidence of some AEs for many erlotinib-related toxicities in the R1507 arms compared with placebo suggests a potentiating effect of the addition of IGF-1R blockade to erlotinib treatment in this population.