SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BO18279)

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 phase II marker identification trial for erlotinib (Tarceva®) in second line NSCLC patients– [redacted] – March 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	This study was conducted in 26 sites in 12 countries: Germany, Hong Kong, Poland, Spain, Taiwan, Bulgaria, Italy, United Kingdom, France, Russia, Singapore and Estonia.		
PERIOD OF TRIAL	29/07/05 – 1/12/06 (data cut-off)	CLINICAL PHASE	II
OBJECTIVES	The primary objective was the identification of differentially expressed genes that are predictive for benefit of erlotinib treatment. The secondary objective were to assess alterations in the EGFR signaling pathways with respect to benefit from treatment.		
STUDY DESIGN	An open label, non-randomized phase II study		
NUMBER OF SUBJECTS	264		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with histologically documented advanced NSCLC, with PS 0-2, who had failed at least one course of standard chemotherapy or were unsuitable for chemotherapy, and whose tumor was accessible to biopsy by bronchoscopy.		
TRIAL DRUG / STROKE (BATCH) No.	Erlotinib 150mg: [redacted] Erlotinib 100mg: [redacted] Erlotinib 25mg: [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	Erlotinib 150 mg, once daily, by mouth		
REFERENCE DRUG / STROKE (BATCH) No.	N/A		
DOSE / ROUTE / REGIMEN / DURATION	N/A		
CRITERIA FOR EVALUATION			
POTENTIALLY PREDICTIVE MARKERS	• Assessment of gene expression profiles in tumor tissue and normal cells • Gene mutation analysis for EGFR and other molecules involved in EGFR signal transduction • Other marker assessments that may correspond with erlotinib efficacy		
EFFICACY	• Overall response and clinical benefit rates assessed by using RECIST criteria • Time to progression (TTP), progression-free survival (PFS) and overall survival		
SAFETY:	• Adverse events and serious adverse events • Laboratory tests		

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STATISTICAL METHODS	The primary goal of the analysis was to find a set of candidate transcripts differentially expressed between clinically benefiting patients (PR+ CR + SD maintained > 12 weeks) and not clinically benefiting patients (PD + non durable SD < 12 weeks). Each transcript was analyzed separately using the Student t-test and the Wilcoxon sum of rank test. Multiple testing corrections were via an FDR control approach. The study was powered to realistically identify straightforward markers of clinical benefit. The secondary goal, more exploratory, was to assess the ability of the expression pattern to predict the clinical benefit, using multivariate classification analyses. Additional exploratory biomarker analyses, based on data from IHC and FISH scores as well as the DNA mutation data, were performed to explore the potential of those markers to predict clinical benefit and/or toxicity.

METHODOLOGY:

The clinical evaluations of each patient were performed as described in the schedule of assessments (Table 3, page 35 in the report body). After screening patients proceeded to the baseline visit as soon as they were confirmed as acceptable and all selection criteria were met. At the BL visit a full work-up took place and the tumor samples were taken via bronchoscopy.

Day one of the study was the day when the patient took study drug for the first time. Patients took medication each morning at approximately the same time one hour before food intake or two hours after with up to 200 ml of water by mouth.

At the BL visit, a biopsy was performed to collect tumor tissue.

The first sample was frozen in liquid nitrogen immediately after tissue removal to prevent RNA degradation. RNase free utensils were used. This sample was used for gene array analyses.

The second tumor sample was formalin fixed and embedded in paraffin. This formalin fixed paraffin embedded (FFPE) block was used for DNA sequencing and IHC analyses.

Two blood samples of 2.5 mL each were collected into a RNA stabilizing reagent.

If a tumor block was available from initial diagnostic procedures, this tumor block was provided. If the tumor block could not be provided, 10 tissue sections (unstained, uncovered slides) were provided. Molecular analyses were performed on this initial diagnosis tissue as well. If no histology was done for primary diagnosis, the patient was still eligible for this study.

If safely obtainable (1st and 2nd tumor sample) or available (tumor block from initial diagnosis) these 4 samples mentioned above were mandatory for all patients entering the study.

STUDY VISITS:

After the baseline visit, patients were evaluated as described in the schedule of assessments. Safety assessments (laboratory tests and adverse event recording) were done on a regular basis.

TISSUE ANALYSES:

Tumor tissue was microdissected and processed for gene expression analysis by Affymetrix gene chips. Results were compared to the clinical outcome of the patients and was then separated into a benefiting and non-benefiting patient population. The DNA mutation status of the genes encoding EGFR and KRAS was analyzed by DNA sequencing. Gene copy number of EGFR was studied by FISH.

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PREDICTIVE MARKER RESULTS

The primary objective of this study was to identify 'binary' marker of clinical benefit. The study was powered to detect five genes with eight-fold change in gene expression for clinical benefit vs. no clinical benefit. Affymetrix gene expression profiles were primarily analyzed to identify differentially expressed genes between the patients who derived clinical benefit status and those who did not. Using False Discovery Rate statistical criteria, no gene was identified as a marker for clinical benefit. In exploratory analyses 8 potential candidate markers for response were identified (EGFR, PSPH, RAPGEF5, GBAS, SCYL3, DKFZP686M0199/SERF1A, LANCL2, LRRC31), as well as 5 potential candidate markers for clinical benefit (PTPRF, PTP4A1, STCH, SFRS7, RARRES1).

EFFICACY RESULTS

Partial tumor response was shown in 14% of patients and stable disease in 30%. The median PFS was 11.3 weeks (95% CI 8-12 weeks) and the median overall survival was 7.6 months (95% CI 7-9 months). In this study there were 6 patients with EGFR mutations (L858R/ exon 19 deletion). Four of these 6 patients experienced PR and 2 had SD. All patients with EGFR mutations experienced clinical benefit from erlotinib treatment. A total of 10 patients (9 from bronchoscopic sample, 1 from initial diagnosis sample) in this study had KRAS mutations (codons 12, 13, 61). Four of these patients experienced SD, 5 had PD and 1 had no data. The number of patients with KRAS mutations was small; therefore, it is difficult to draw meaningful conclusions from comparisons of mutation status with efficacy outcome. Interesting, however, 2 patients with KRAS mutations did obtain clinical benefit from erlotinib. Further studies are needed to give a more definitive answer to the question of whether patients with KRAS mutations can derive survival benefit from erlotinib.

SAFETY RESULTS:

Eighty-eight percent of patients had ≥ 1 adverse event. Forty-one percent had at least 1 grade ≥ 3 adverse event. Seventy-five percent of patients had ≥ 1 treatment related adverse event. The most common adverse events experienced by patients were rash, diarrhea, dyspnoea and anorexia. Twenty-four percent of patients had a serious adverse event. Dose reductions were required by 11% of patients and 6% discontinued due to an adverse event.

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CONCLUSIONS:

MERIT is the largest, global, multi-centre gene-profiling study ever performed in NSCLC. The findings support the use of erlotinib in patients with advanced NSCLC who have failed ≥1 chemotherapy regimen or who are unsuitable for chemotherapy.

No binary markers for clinical benefit were identified at the RNA expression level in baseline tumour biopsy samples as part of the primary analysis. In exploratory analysis 8 potential markers for response were identified as well as 5 potential markers for clinical benefit.

Although patients with EGFR mutations tended to have higher response rates, too little data are available on these or from patients with KRAS mutations to enable firm conclusions to be drawn. In a single arm study predictive and prognostic effects cannot be distinguished and so no conclusions can be made on the applicability of EGFR IHC or FISH as biomarkers predictive of benefit from erlotinib.