Non-Interventional Study (NIS) Report Synopsis	
Drug Substance	Gefitinib
Study Code	NIS-ODE-DUM-2009/1
Edition Number	Version 4.0
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REASON:
An NIS Registry for the Epidemiological and Scientific evaluation of EGFR mutation status in patients with newly diagnosed locally advanced or metastatic NSCLC (Stage IIIB/IV non-small cell lung cancer)

Study dates: First subject enrolled: 09 November 2009
Last subject last visit: 31 October 2012

Phase of development: Non-Interventional Study (NIS)

This non interventional study was performed in accordance with Good Clinical Practice.

Rationale

This study was intended to generate key data on the prevalence of EGFR mutation status and its association with major clinico-pathological parameters derived from a sufficiently large sample of stage IIIB/IV NSCLC patients with a predominantly Caucasian ethnic background in Germany. It had been envisaged that these data will facilitate and support the design of future clinical pathways and subsequent decision making in the treatment of patients with stage IIIB/IV NSCLC. In addition, the study was to provide valuable insight into current treatment patterns in lung cancer patients in Germany as well as the associated resource use and quality of life. It had been envisaged that the results of this study would make a significant contribution to the existing knowledge regarding the pathology, time course and management of patients with stage IIIB/IV NSCLC.

Study centres

149 centres in Germany, 127 hospitals and 22 oncologists in private practice;

Publications

There are no full publications at the time of completion of this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Epidemio-logical	To collect epidemiological data on EGFR mutation status (mutation positive, M+; no EGFR mutation, M-) in a population of predominantly Caucasian ethnicity and to correlate EGFR mutation status with clinico-pathological characteristics (e.g. smoking status, sex, histology, etc). In particular, the study aimed to determine the frequency of EGFR M+ lung cancers in patients with clinico-pathological characteristics that are not commonly associated with EGFR mutation positivity (i.e., smokers, men, and non-adenocarcinoma).	**EGFR mutation status** was the main criterion for evaluation, notably: 1) Epidemiological data on EGFR mutation status (M+, M-), including EGFR status, - tissue type/localisation used for mutation testing, exon specification, pathology institute that performed the test, turnaround time of tests, methodology used for testing, origin of tissue used for testing, performance of further analyses; 2) The correlation between EGFR mutation status and clinico-pathological characteristics including gender, smoking status, and histology;

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To collect real-life clinical outcome data in all EGFR M+ patients up to and including progression and death (e.g. PFS, OS, ORR (former DCR); descriptive statistics only);	**Progression-free Survival (PFS)** was defined as the period from therapy start to the date of the earliest sign of disease progression or death of any cause as documented on the Tumour evaluation form or on the Study discontinuation form and the form Physician contact/ Hospitalisation of the eCRF. Patients who were alive without progression at the end of observation were right censored and entered into the analysis with time from therapy start to the last observation date. As this is a non-interventional design, the type of response was documented according to the radiologist's report (and not according to pre-specified criteria) and could be radiological or clinical, as judged by the investigator. A formal evaluation per RECIST criteria was not part of this study, also, intervals for follow-up investigations were not specified. Thus, data is not comparable with data from clinical studies. **Overall Survival (OS)** was defined as the period from the date of therapy start to the date of death of any cause as documented on the study discontinuation form of the eCRF. Patients who were alive at the end of observation were right censored and entered into the analysis with time from therapy start to the last observation date. **Objective Response Rate (ORR)** was defined as the percentage of patients with complete response or partial response on the Tumour evaluation form as best response. As this is a non-interventional design, the type of response was documented according to the radiologist's report (and not according to pre-specified criteria) and could be radiological or clinical, as judged by the investigator. A formal evaluation per RECIST criteria was not part of this study.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Pharmaco-economical	To collect real-life pharmacoeconomic data (resource use) associated with the diagnosis and treatment of EGFR M+ patients. Data collected included but were not limited to the following: Resource use for disease-progression, treatment of side-effects and disease-related-symptoms, hospital admissions (disease-related, other reasons), special therapeutic procedures (e.g. radiotherapy, chemotherapy, other therapeutic modalities), primary care visits (disease-related, other reasons), outpatient visits (disease-related, other reasons), concomitant medication (disease-related, AE-related), other care (rehabilitation therapies, community-based care, home visits by doctors, nurses, etc), terminal care (home, hospital, hospice), data on work productivity, and out-of-pocket expenditures (disease-related, AE-related).	Real-life pharmacoeconomic data (resource use) associated with the diagnosis and treatment of EGFR M+ patients included but were not limited to the following: Resource use for disease-progression, treatment of side effects and disease-related symptoms, hospital admissions (disease-related, other reasons), primary care visits (disease-related, other reasons), outpatient visits (disease-related, other reasons), concomitant medication (disease-related, AE-related), other care (rehabilitation therapies, community-based care etc.), data on work productivity, and out-of-pocket expenditures (disease-related, AE-related).
Secondary		To collect real-life data on first-line treatment decisions in EGFR M+ and M-/Mx patients To collect real-life data on 2nd-line and further treatment decisions in EGFR M+ patients	Outcomes in terms of real-life treatment patterns included: First-line treatment decisions in EGFR M+ and M-/Mx patients, including substance, type of medical care centre and reason if no treatment was performed as documented on the first-line therapy form of the eCRF at visit 2. • EGFR M+ patients: change of first-line therapy as documented on the first-line therapy form of the eCRF at additional follow-up visits. • EGFR M+ patients: planned maintenance therapy as documented on the first-line therapy form of the eCRF at additional follow-up visits. • Concomitant therapy to the anti-tumour therapy by antiemetics, folic acid, G-CSF, steroids or vitamin B12 as documented on the first-line therapy form of the eCRF at additional follow-up visits. Planned 2nd-line and further treatment decisions in EGFR M+ patients as documented on the therapy form at additional follow-up visits or the study discontinuation form of the eCRF;

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety	To collect safety and tolerability data. In addition this study was to collect real-life data on supportive treatments and AE-management associated with specific first-line treatment regimens in EGFR M+ patients.	Safety and tolerability including real-life data on supportive treatments and AE management associated with specific first-line treatment regimens were evaluated only in EGFR M+ patients with gefitinib treatment. The safety analysis comprises all documented adverse events by taking only adverse events from the corresponding AE and/or SAE section into account. Only adverse events with a date/time of onset later or equal to the start date of the gefitinib therapy were taken into account in the AE analysis. Those AEs with a date/time of onset before this start date or with missing information on date/time of onset were only listed. If a patient had experienced more than one AE and at least one of the AEs was considered by the physician as being related to the gefitinib therapy, the patient was counted as having had an Adverse Drug Reaction (ADR). The same AE (i.e., the same Common Toxicity Criteria [CTC] symptom) reported more than once for a single patient was counted as one AE. If an AE occurred more than once for a single patient, the AE with the highest reported toxicity to gefitinib (CTC grading) was used in the AE analysis.

Study design

National multi-centre prospective observational study

Target subject population and sample size

In order to obtain estimates for EGFR mutation rates with a 95% confidence interval of no more that +/- 5% around the point estimates, an initial sample size of approx. 4,000 patients was required.

In total, 4,243 adult subjects were included with histologically confirmed stage IIIB/IV NSCLC for whom testing of EGFR mutation status was planned.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

n/a.

Duration of treatment

In this non-interventional trial the course of the first-line treatment of EGFR mutation positive (EGFR M+) subjects was observed. Protocol amendment 3 extended the observation of this population to cover further treatment lines. The extended scope of documented data was separately consented by the subjects and was subject to a data cut off at 31st OCT 2012.

Statistical methods

Evaluation of data was performed with descriptive methods of statistics by means of frequency tables and cross tabulations. 95% confidence limits of proportions were calculated to determine precision of results.

Correlations of EGFR mutation status with clinico-pathological characteristics were analysed using a logistic regression model. Secondary endpoints related to clinical outcome, safety and tolerability, and pharmacoeconomic data (resource use) were also evaluated using descriptive statistics.

Number of subjects:

The primary objective of the study was to collect epidemiological data on EGFR mutation status (M+, M-, Mx) in a population of predominantly Caucasian ethnicity and to correlate EGFR mutation status with clinico-pathological characteristics (e.g. smoking status, sex, histology, etc). Sample size estimates were based on a proportion of unevaluable test results of 25%. Of 4,000 eligible patients 2,640 patients were estimated to be EGFR mutation negative (M-), 1,000 patients EGFR mutation unknown / non-evaluable (Mx), and 360 patients EGFR M+.

Furthermore, sample size was dimensioned to reach high precision of estimates of EGFR mutation status overall and within subgroups of patients defined by certain clinico-pathological characteristics (eg, histology, smoking habits and gender). The sample size calculation for this study was performed with the aim to obtain estimates of EGFR mutation rates with a 95% confidence interval of no more that +/- 5% around the point estimates. In the subgroup with the smallest expected sample size (300 never smokers with known mutation status) the uncertainty does not exceed 5.5% (95% CI from 34.5% to 45.5%).

Subject population

A total of 4,243 patients were registered for the study; 4,200 of these were included in the analysis population for the primary outcome. Results of the EGFR mutation testing were available for all of these 4,200 patients (M-: 3,593 (85.5%), M+: 432 (10.3%), Mx: 175 (4.2%)). Of these, 4,196 patients (M-: 3,590 (85.6%), M+: 431 (10.3%), Mx: 175 (4.2%)) fulfilled all in- and exclusion criteria and therefore are included in the evaluation of secondary endpoints like real-life treatment patterns. EGFR M- patients participated in the study until documentation of their first-line treatment decision, likewise patients with non-evaluable mutation status (EGFR Mx) and patients who were tested EGFR M+ but wished to participate in other interventional studies or did not receive first-line treatment. Of the 431 patients who were tested EGFR M+, 42 wished to participate in interventional studies at the time of their first-line treatment decision and 55 were documented to having not received any

first-line treatment. First-line treatment was documented for the remaining 334 EGFR+ patients, who then continued in the study. 320 EGFR M+ patients were assessed at follow-up visits; 206 of these (64.4%) received gefitinib during their first-line therapy, either by starting with gefitinib or by switching during the first line prior to progression.
The patients' ethnic origin was predominantly Caucasian (99.5%); their mean age was 66 years. Most patients (62.1%) were men; the proportion of men was markedly lower in EGFR M+ patients (38.4%) than in EGFR M- patients (64.8%). The mutation cohorts were well balanced with regard to age, BMI and ethnicity. 85.1% of patients were diagnosed with Stage IV disease and 14.7% were Stage IIIB. The predominance of patients diagnosed as Stage IV was most pronounced in the EGFR M+ cohort.

The observation period was terminated on 31st of October 2012 (data cut off date).

Summary of efficacy results

The primary objective of the study was to collect epidemiological data on EGFR mutation status (M+, M-, Mx) in a population of predominantly Caucasian ethnicity and to correlate EGFR mutation status with clinico-pathological characteristics (e.g. smoking status, gender, histology, etc).

Efficacy results were obtained by collecting real-life clinical outcome data in all EGFR M+ patients up to and including progression and death (secondary objective).

The median progression free survival (PFS) and the median overall survival (OS) in the 320 EGFR M+ patients were 9.1 and 17.2 months, respectively. Patients who received a TKI prior to first progression had a median PFS of 10.1 months (95% Cl [8.9-11.7]) and patients who did not receive a TKI prior to first progression had a median PFS of 7 months (95% Cl [5.1-9.4]). EGFR M+ patients who received a TKI at some point during the entire treatment phase (first-line and further) had a median OS of 18.4 months (95% Cl [16.3-21.8]) and patients with EGFR mutation not treated with a TKI at any time point during their therapy has a median OS of 13.6 months (95% Cl [9.3-15.4]). In addition, OS and PFS were longer in women than in men, and tended to be longer in never-smokers than in current/former smokers.

In accordance with the real-life treatment pattern to be captured in the course of the non-interventional study, the observation time points were not prespecified and followed the decision of the treating physician. Consequently the duration of stable disease which is a prerequisite to determine the disease control rate could not be ascertained appropriately. However, the available clinical data allowed the calculation of the objective response rate (ORR) instead. Calculated ORR based on routine tumour evaluation frequencies was 51%. EGFR M+ patients who received first-line treatment with EGFR inhibitors achieved an ORR of 53.6% ; whereas EGFR M+ patients who received a chemotherapy and no TKI achieved an ORR of 45%. ORR was higher in women than in men, higher for never-smokers than current/ former smokers and also higher in patients with adenocarcinoma.

Summary of real-life treatment patterns

Overall, the majority of patients (84.9%) were treated at a hospital, most often (59.8%) in an inpatient setting. The remaining patients treated at a hospital were outpatients (27.8%) or received daytime care (12.4%). 14.3% of patients were treated by an oncologist in private practice. The data of all NSCLC patients reflects the distribution of medical care centres in the large cohort of EGFR M- patients. The settings of medical care for EGFR M+ patients largely resembled those of the total population: most (81.7%) were treated at a hospital. However, a greater percentage (54.2%) was treated as outpatients and a lower percentage (32.6%) as inpatients.

First-line treatment was administered in 3,320 of 4,196 NSCLC patients (79.1%). 374 of the 3,320 patients receiving first-line treatment wished to participate in another clinical study and were not included for evaluation of secondary outcomes. No first-line treatment was given in 867 patients (20.7%). First-line therapy was performed in 376 of 431 EGFR M+ patients (87.2%), with 42 (9.7%) participants entering into interventional studies. For 2800 of 3590 EGFR M- patients a first-line therapy was specified (78.0%); 319 (8.9%) of them participated in other interventional studies.

Most first-line treatment decisions in the M- patients (multiple counts) were made in favour of carboplatin (48.5%), followed by cisplatin (36.2%), pemetrexed (30.4%), gemcitabine (24.3%), and vinorelbine (23.6%). The choice of gefitinib for first-line treatment in the M- cohort was made in 5.7% of patients. Regarding the EGFR M+ patients, at the time of the primary first-line treatment decision most received gefitinib (53.0%), followed by carboplatin (22.2%) and cisplatin (18.0%).

Most study patients (73.6%) received chemo-combination therapy as a primary first-line treatment, followed by mono-chemotherapy (11.9%) and TKI (8.2%). The primary first-line treatment decision was different in the EGFR M+ and EGFR M- cohort: 56.6% of EGFR M+ patients were documented to be treated with TKI and 35.0% with chemo-combination therapy. In contrast, 78.5% of EGFR M- patients received chemo-combination therapy and 12.9% mono-chemotherapy.

Summary of pharmacoeconomical endpoints

Pharmacoeconomic data was collected for the period of first-line treatment until first progression. Descriptive statistics were performed for the subgroups receiving first-line therapy: 1) Patients with chemotherapy, 2) Patients with TKI therapy, 3) Patients with therapy switch. These subgroups are relevant for the evaluation of economic efficiency of the treatment of EGFR M+ patients in a real-life setting, since they display the therapy regimens available and provide a basis for the descriptive comparison. The direct comparison of the three subgroups indicates that the highest average outpatient and inpatient costs were documented for chemotherapy patients within the observation period. However, the average drug costs are highest for TKI patients in comparison to chemotherapy and switch patients. Descriptive statistics was performed with respect to first-line therapy costs, nursing auxiliary and incapacity to work.

Summary of safety results

222 patients received gefitinib during their study participation and were therefore analysed for safety. At least one adverse event was recorded for 129 patients (58.1%). SAEs were reported for 49 patients (22.1%); 8 patients (3.6%) had AEs leading to treatment discontinuation; 11 deaths (5% of patients) were documented.

Of the 11 documented deaths, one patient died of bronchopulmonary hemorrhage 94 days after first administration of gefitinib. According to the investigator, the event was related to treatment with gefitinib. The other 10 deaths were not related to gefitinib: 1) myocardial infarction, 2) sudden death (not associated with CTCAE term), 3) lower abdominal pain (multi-organ failure), 4) death (not associated with CTCAE term), 5) death (not associated with CTCAE term), 6) recurrent pneumonia, 7) pulmonary embolism, 8) cerebral haemorrhage, 9) sepsis, and 10) acute myocardial infarction.

Adverse drugs reactions (ADRs) were recorded for half (50%) of the safety population (111 patients treated with gefitinib). In terms of CTC Organ Systems, Dermatology/Skin (41.0%), Gastrointestinal (27.9%), and Ocular/Visual (5.0%) were most commonly recorded. As for CTC symptoms, rash: acne/acneiform (in 23.9% of patients), diarrhea (18.0%), dry skin (10.8%), nail changes and pruritus/itching (6.3% each), and dermatology other symptom (5.0%) were most commonly recorded.

Overall, the safety profile was consistent with the Summary of Product Characteristics (Fachinformation as of April 2012).