Clinical Study Report Synopsis	
Drug Substance	Not applicable
Study Code	D7913L00086
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A molecular ePIdemiOlogy study in Asia patients with advanced NSCLC of adEno histology to assess EGFR mutation status: PIONEER study

Study dates: First subject enrolled: 29 September 2010
Last subject last visit: 31 July 2011

Phase of development: Prevalence study. Interventional

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Patients were recruited from 51 investigational sites in Asia that have expertise in lung cancer diagnosis. (Number of countries: 7, date of 1st patient enrolled: 29 Sep 2010 and last patient completed the study: 31 July 2011)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objective was to assess the EGFR mutation status in Asian patients with NSCLC of adeno histology**.**

Primary objective:

- To assess the EGFR mutation status tested by DNA sequencing, or other methodology deemed appropriate by study sites

Secondary objectives:

- To investigate the correlation between EGFR mutation status and demographic data (including smoking pattern) and disease data in patients with NSCLC of adeno histology
- To investigate the correlation between EGFR mutation status and tissue sampling techniques in patients with NSCLC of adeno histology
- To investigate the attrition factor of EGFR mutation testing
- To investigate the correlation of EGFR mutation status between histology and cytology for patients who provided both samples

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the EGFR mutation status tested by DNA sequencing, or other methodology deemed appropriate by study sites	Overall EGFR mutation status	Statistical Analysis

Objectives	Outcome variables	Type
Secondary	**Secondary**	
1. To investigate the correlation between EGFR mutation status and demographic data (including smoking pattern) and disease data in patients with NSCLC of adeno histology 2. To investigate the correlation between EGFR mutation status and tissue sampling techniques in patients with NSCLC of adeno histology 3. To investigate the attrition factor of EGFR mutation testing 4. To investigate the correlation of EGFR mutation status between histology and cytology for patients who provided both samples		Statistical analysis

Study design

This was an epidemiological, multicenter study of EGFR mutation status in patients with newly diagnosed advanced (Stage IIIb/IV) NSCLC of adeno histology. Approximately 1270 treatment naïve advanced NSCLC patients who fulfilled the criteria were to be recruited by investigational sites throughout Asia. The demographics and cancer tissue/cytology sample were collected after the patient had provided informed consent. All tissue samples were analyzed for EGFR mutations at the designated laboratories using Scorpion ARMS IVD2 test.

Target subject population and sample size

The sample size was calculated basically to obtain a sufficiently accurate estimate of the proportion of EGFR mutation positive patients. It was assumed that the true value of this proportion was 40%. Then the sample size necessary for making a 95% confidence interval based on the Wilson score method for the proportion have the width of less than ±3% around a point estimate should be more than 1047. Taking some patients to be judged as undetermined and feasibility into consideration, the sample size was decided to be 1270.

In addition to the overall analysis, country-specific analyses were also considered. In order to make sure results from the country-specific analyses had a certain level of reliability, the analysis was to be done only for countries with around 100 or more patients because at least 97 patients were necessary to obtain a 95% confidence interval for the proportion of EGFR mutation positive patients that had width of less than ±10% around a point estimate.

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

Not applicable

Duration of treatment

Not applicable

Statistical methods

A statistical analysis plan that describes the details of statistical analysis was prepared before the database lock. Statistical analysis was done by Statistics and Programming of AstraZeneca Japan using SAS 8.2.

Primary end point

The overall mutation status was summarized in terms of the number of patients classified into the three categories of positive, negative and undetermined. The percentages of positive and negative patients were calculated along with corresponding 95% confidence intervals using the Wilson score method. In this percentage calculation, patients with undetermined mutation status were not included in the denominator.

This same analysis was also done by factors such as country, gender, age group, smoking status, pack-year, stage, and histological type and tumour grade. Statistical comparison in proportion of EGFR mutation positive patients between categories for each factor was done. Factors with p-values less than 5% in the univariate analysis stated above were explored by means of multivariate logistic model analysis.

Mutation status for each mutation type was summarized in terms of the number and percentage of mutation positive patients. In this percentage calculation, patients with undetermined mutation status were not included in the denominator.

Subject population

A total of 1510 patients were enrolled and 1488 patients were registered from 51 investigational sites in 7 Asian countries (China, Hong Kong, India, Philippines, Taiwan, Thailand and Vietnam). Out of 1488 registered patients, 1482 patients were included for PPS analysis.

Out of 1482 patients, 839 (56.6%) were males and 643 (43.4%) were females. The mean (SD) age of the patients was 60.0 yrs (12.0) with a minimum of 17 yrs and maximum of 94 yrs. All except one patient were Asian and 73.8% (n=1093) patients belonged to the Chinese ethnic group.

The total number of patients who never smoked was 779 (52.6%), ex-smokers were 310 (20.9%), occasional smokers were 66 (4.5%) and regular smokers were 327 (22.1%). Among the patients with a positive smoking history (n=695), the mean (SD) pack years was 34.6 (31.0).

For 94.3% (n=1398) of patients, the time interval between the original diagnosis and enrolment into the study was <6 months. At original diagnosis, disease metastasis was found

in 1175 (79.3%) patients, locally advanced disease in 270 (18.2%) patients and others in 37 (2.5%) patients.

The most common site for biopsy was lung (984 patients), local lymph nodes (119 patients) and other (121 patients). The most common method of biopsy was image-guided core biopsy (354 patients), bronchoscopic biopsy (295 patients), incisional biopsy (123 patients), lobectomy (111 patients) and cytology (90 patients). Tissue sample was taken from primary tumour for the majority of patients (1012 patients) and sample processing was done using 10% neutral buffered formalin.

Summary of efficacy results

A total of 1482 patients were included in the PPS of which EGFR mutation test was successful in 1450 (97.8%) patients and undetermined in 32 (2.2%) patients. Among 1450 successful patients, EGFR mutation status was positive in 746 (51.4%) patients and negative in 704 (48.6%) patients.

Table S2 Overall judgement of EGFR mutation status (PPS)

Overall judgment on EGFR mutation status	Number (%) of patients N=1482		95% CI of %
Positive (at least one mutation within exon 18-21)	746	(51.4)	48.9 - 54.0
Negative (no mutation within exon 18-21)	704	(48.6)	46.0 - 51.1
Undetermined	32		

For patients who provided both of histology and cytology samples, test results from histology samples were used.

The following factors were evaluated for positive EGFR mutation status:

Country (China, Hong Kong, India, Philippines, Taiwan, Thailand, Vietnam) as a factor showed statistical significance with a p-value of <0.001. In India, EGFR mutation status was positive in only 22.2% of patients while in Taiwan and Vietnam EGFR mutation status was positive in 62.1% and 64.2% respectively.

Gender as a factor showed statistical significance for positive EGFR mutation status with a p-value of <0.001 with higher incidence in females (61.1%). Ethnicity (Indian, Chinese, Japanese, Thai, Kinh, Malay and Mixed/other ethnicity group) as a factor showed statistical significance with a p-value of <0.001 by Fisher's exact test.

Smoking as a factor showed statistically significant p-value of <0.001 with higher incidence of positive mutation status in those patients who never smoked (60.7%). Pack years emerged as a statistically significant factor for positive EGFR mutation status with a p-value of 0.001.

Disease stage at original diagnosis emerged as a statistically significant factor with a p-value of <0.001 with higher incidence of positive mutation status in metastatic group (53.9%). Distant metastases appeared as a statistically significant factor with a p-value of <0.001 by

Fischer's exact test. Disease stage classification as a factor showed statistical significance (p=0.009).

Age group, time from original diagnosis, method of diagnosis, malignant pleural effusion, primary tumour, regional lymph nodes and tumour grade emerged as statistically non significant factors for the positive EGFR mutation status.

Under multivariate logistic regression model analysis for overall judgement of EGFR mutation status, ethnic group as a factor was statistically significant with a p-value of <0.001. The Indian population had less chance of having positive mutation status than other populations. Pack years of 10< - 30 (OR; 0.51) and >30 (OR; 0.26) were compared with 0 – 10 pack year for overall judgement of EGFR mutation status. All the pack years >10 had less chance of having positive mutation status than 0 - 10 pack year. Pack year emerged as a statistically significant factor with a p-value of <0.001.

The most common mutations were exon 19 deletion and L858R point mutation seen in 352 (24.3%) and 332 (22.9%) patients respectively.

The mean (SD) time interval taken for reporting the mutation test was 17.6 (13.3) days with a range from 1 day to 148 days.

Twenty-three patients provided both histology and cytology samples. Among these 21 had concordant EGFR mutations status and 2 had mutation results that did not match.

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

Not applicable.