Clinical Study Report Synopsis

Drug Substance	Gefitinib
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An International Expanded Access Clinical Programme with ZD1839 (IRESSA) for Patients with Advanced Non-small Cell Lung Cancer (NSCLC)

China amendment 1: A study on the long term survivals in an Expand Access Program (EAP) of Iressa

Study centre(s)

This study was conducted in 15 centres in China. These centres are those participated in the EAP and are still following patients according to the EAP protocol at the time of study initiation.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
The primary objective is to describe the quality of life of long-term survivors who are not terminated from the EAP.	Quality of life will be measured by the FACT-L total score, TOI and LCS score generated from FACT-L questionnaire.
Secondary	**Secondary**

Objectives	Outcome variables
1. To collect the risk factors related to prognosis in addition to the information already collected from EAP (age, gender, histology, smoking history, previous history of anti-cancer treatment, response to prior chemotherapy, disease stage before starting gefitinib treatment, current PS*, anti-cancer treatment after entering EAP)	1. The proportion of the risk factors will be described.
2. To describe the current tumour control status via RECIST*	2. The current tumour control status will be described by the best overall objective response rate (CR+PR/total), disease control rate (CR+PR+SD/total), and duration of response (defined from the response was observed till objective disease progression was confirmed).
3. To describe the treatment compliance of gefitinib in these patients	3. To describe the treatment compliance of gefitinib in these patients (number of gifitinib pills distributed divided by the days of follow-up).
4. To describe the current clinical status of long-term survivors in the EAP program by clinical examinations. *	4. The current clinical status will be described by clinical examinations*.
5. To compare the key clinical features in fast-progressers versus long-term survivals.	5. To compare the key clinical features (age group, gender, histology, smoking history, treatment-naive or pre-treated, response to prior chemotherapy,) in fast-progressers (defined as no more than 1 follow-up visit after recruitment with the reason of discontinuation being “disease progression”) versus long-term survivals.
Exploratory objectives*	**Exploratory objectives**
1. To describe the EGFR gene mutation status in tumour tissue and peripheral blood samples of the long term survivors in the EAP program.	1. The proportion and nature of mutation in EGFR will be described by analysing DNA from tumour tissue and from circulating DNA extracted from peripheral plasma.
2. To detect Ki-67 protein expression in tissue by IHC for association with survival.	2. Ki-67 protein expression status in tumour tissue will be analysed for association with survival.

* applies to the active patients in EAP.

Study design

This is a descriptive observational study, in which data are collected in an epidemiological way. For patients who are actively participating in the EAP and are still on gefitinib treatment, data will be collected in a cross-sectional manner to reflect the current status. For patients who had been on gefitinib treatment for more than 3 years but have already terminated from EAP, data will be collected in a retrospective manner.

Target subject population and sample size

A total of 934 patients were screened in EAP database and the target population was the long-term survivors who have been receiving gefitinib for more than 3 years in EAP. We plan to collect the clinical data to analyse the characteristics of these long-term survivors on gefitinib treatment, and collect quality of life and safety data on the active long-term patients in the EAP.

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

NA.

Duration of treatment

NA.

Statistical methods

The study is generally descriptive in nature and no statistical assumption was set. The key clinical features between the fast-progressers and long-term survivors will be compared by chi-square test in an exploratory fashion. Two-sided test will be used with a significance level of 0.05, and all confidence interval is 95% unless otherwise specified. Continuous variables will be analyzed using mean, std, median, Q1, Q3, minimum and maximum values. Categorical variables will be analyzed using the frequency and percentages. The missing values will not be handled.

Subject population

A total of 934 patients were screened in EAP database. 25 of them were active long-term survivors and 34 of them were long-term survivors terminated from EAP. These 59 patients were enrolled from 15 centers in China. The data of 875 fast-progressers were extracted from the existing EAP database.

Among the 25 active long-term survivors, 22 plasma and 3 tissue samples were collected from 24 patients and only one of the 24 patients provided both tissue and blood samples.

Summary of efficacy results

Among the 25 long-term survivors, the mean FACT-L Score was 62.88, the mean TOI score was 36.46 and the mean LCS score was 12.79. In PWB, for question “I have a lack of energy”, 70.8% patients felt no lack of energy, and 20.8% patients felt a little bit lack of energy. In FWB, for question “I am able to enjoy life”, 50.0% patients were able to enjoy life very much, and 29.2%

patients were able to enjoy life quite a bit. For question "I am content with the quality of my life right now", 62.5% patients were content with the quality of their life very much, and 12.5% patients were content with the quality of their life quite a bit.PS 0-1 accounted for 91.66% when they were evaluated in the cross-sectional survey. Therefore, patients still have a good QoL even after more than 3 years gefitinib 250 mg treatment.

Age<65 years (68.52%), adenocarcinoma(81.36%), female(55.39%) and never-smoker(70.69%) accounted for the majority of long-term survivors. The requirement of concomitant treatment was 28.07% in long-term survivors during gefitinib treatment. Patients who had achieved longer survival with gefitinib treatment maintained good PS (PS 0~1 was 91.66%).

For those active long-term survivors, the objective response rate was 37.5%, the disease control rate was 87.5% and the median duration of response time was almost 68 months, which demonstrated good efficacy of gefitinib.

The percentage of female was higher in long-term survivor group compared with fast-progressers, (55.93% vs 40.81%, P=0.0227). Though the percentage of patients with stage I and stage II in long-term survivor group was higher than that in fast-progressers group (5.45% vs 0.00%), the clinical stage differences was significant (P=0.0002). The result might due to the dramatic difference of sample size between the two groups.

Only 3 tissue samples were collected from the 24 long-term survivors who consented to participate in the exploratory research. 1 was EGFR mutation positive in the 3 tissue samples. 22 blood samples were collected from the 24 long-term survivors and 1 was tested with EGFR mutation positive. There was only one long-term survivor who was a female never-smoker with stage IV and adenocacinoma provided tumour tissue and plasma sample. The EGFR mutation status of the patient was negative in her tissue and blood samples.

In this study, the Ki67 protein expression was tested in the 3 tissue samples. 2 of them were Ki67 protein expression positive and the response duration time of the 2 patients was over 73 months.

Summary of pharmacokinetic results

NA.

Summary of pharmacodynamic results

NA.

Summary of pharmacokinetic/pharmacodynamic relationships

NA.

Summary of pharmacogenetic results

NA.

Summary of safety results

In long-term survivors terminated from EAP group, no adverse event was reported. In active long-term survivor group, 2 adverse events were reported for 1 (4%) subject. One adverse event was diarrhea and the other was rash, which were generally consistent with its prescribing information. No serious adverse events and adverse events leading to termination or death were reported in active long-term survivor and long-term survivor terminated from EAP groups. No new safety concerns for gefitinib have been identified from the laboratory parameters. The majority of ALT, AST and creatinine abnormities were mild to moderate.