Non-Interventional Study (NIS) Report Synopsis	
NIS Name/Code	NIS-OGB-IRE-2012/1
Edition Number	1
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A multicentre, retrospective chart review study to characterise gefitinib usage and outcomes in routine treatment

Drug Substance:	Gefitinib
Developmental Phase:	Non-interventional study
Study dates:	January 2013 - October 2013
Study Completion Date:	31st Oct 2013

Background

The outcomes of treating patients with gefitinib have been assessed in randomised clinical trials predominantly in Asian patients. The aim of this study was to assess real world gefitinib usage patterns, patient characteristics and outcomes in a routinely treated UK population.

Objectives:

Primary objective

To assess treatment duration as a surrogate of Clinical Benefit (CB) and Overall Survival (OS) in a 'Real World' population treated with gefitinib.

Secondary objectives

- To assess treatment duration and OS in the subgroup of patients of Caucasian ethnicity and in the subgroup of patients treated with gefitinib for at least three months.
- To describe the characteristics of patients treated with gefitinib for all patients and stratified by whether gefitinib discontinued treatment before or after three months.
- To describe treatment patterns in patients treated with gefitinib (prior chemo, treatment breaks, treatment on discontinuation).
- To assess duration of treatment and OS in patients stratified by age, gender, stage and performance status.

Methods

An observational, retrospective, descriptive non-interventional study (NIS) of patients with locally advanced or metastatic EGFR mutation positive NSCLC previously treated with gefitinib in routine clinical practice.

Baseline characteristics were summarised descriptively; time to discontinuation and overall survival were assessed using Kaplan-Meier and Cox regression models. Subgroup analyses were based on clinical benefit (CB) $\geq$ 3months treatment and Caucasian ethnicity.

Study Population

Inclusion criteria

The subject population that was observed in the NIS fulfilled all of the following criteria:

- Patients who received gefitinib first line in the UK Single Payment Access (SPA) scheme.
- Locally advanced or metastatic EGFR mutation positive non-small cell lung cancer (NSCLC).
- Supplied with first pack of gefitinib prior to 1st April 2012.

Exclusion criteria

- Patients treated privately (i.e. outside the National Health Service).
- Gefitinib was second-line therapy following treatment failure on a prior therapy.

Results

The majority of patients included in the study were female (61%) and Caucasian (74%) and aged 70 years (95%CI 68 to 72); gender, ethnicity and age were generally balanced between patients with and without CB. In the overall sample, 40% of patients were non-smokers (i.e. never-smokers), 36% were ex-smokers and 10% reported to be current smokers. A higher percentage of patients with CB compared to those without CB (41% vs 34%) were non-smokers.

Out of 202 patients, 24 (12%) were fully active (PS0), 85 (42%) were restricted in physically strenuous activity (PS1), 54 (27%) were ambulatory and capable of all self care (PS2) and 12 (6%) were capable of only limited self care (PS3). The proportion of patients with PS0 or 1 was greater for

patients with CB and the proportion of patients with PS 2 or 3 greater for patients without CB. Notably 4% of patients with CB were PS3 compared to 12% of patients without CB.

Approximately 84% of patients had stage IV NSCLC at the time of diagnosis, most had only one metastasis (45%) and the most common site of metastases was the lung (75% of patients with stage IV NSCLC), followed by bone (35%) and lymph nodes (18%). There were more patients with brain only metastases in patients without CB (15% vs. 2%). In the overall study sample, the most common histology was adenocarcinoma, present in the majority of patients (88%) in the overall population, 81% of patients without CB and 90% of patients with CB.

Overall approximately 70% of patients had not received any previous treatment. Of those that had a previous treatment, 68 % reported radiotherapy, 36% surgery and 7% chemotherapy. The majority of patients received previous radiotherapy as palliative, rather than adjuvant treatment.

The majority of patients (90%) did not have any change in gefitinib dosing schedule. Of the 177 patients who progressed 26% received doublet chemotherapy, 5% were treated with another EGFR TKI and 66% received best supportive care.

The overall mean time until treatment discontinuation was 11.8 months (95%CI 10.4 to 13.2 months). Stratifying by CB, mean time to discontinuation for patients receiving treatment for <3 months was 1.4 months (95%CI 1.2 to 1.6months) whereas mean time to discontinuation for patients with CB was 14.4 months (95%CI 12.9 to 15.9 months) (p 0.0001). Stratifying by ethnicity the mean time until treatment discontinuation was 11.4 months (95% CI 9.8 to 13.1months) for Caucasian patients was, compared with 12.6 (10.1; 15.2 months) for patients of other ethnicities.

The Cox regression model included treatment discontinuation as the dependent variable and ethnicity, gender, age, stage (at diagnosis), and performance status as covariates. There was no difference associated with ethnicity and only PS1 vs PS3 was significantly associated with a greater time to discontinuation. This suggested that only differences in PS in terms of PS1 (restricted in physically strenuous activity) compared with patients of PS3 (capable of only limited self care) were significantly associated with differences in rate of discontinuation (HR 0.42 [95%CI 0.21 to 0.84]). PS1 patients received treatment for longer than PS3 patients; however median treatment duration for PS3 patients was 3.9 months (95% CI 1.0 to 11.0 months). No other statistically significant differences were observed.

Of the 202 patients included, 44 (22%) remained alive at time of data collection, 74% died before data collection and survival status was unknown in 5% of patients. The main recorded primary cause of death was NSCLC itself (56%). A further 4% of patients died due to other cancer-related complications, 4% died due to other reasons (non-cancer related) whilst the primary cause of death remained unknown for 35.6% of patients.

The mean time until death was 16.4 months (95%CI 14.9 to 17.9 months). Stratifying by CB, mean survival time for patients receiving treatment for 3 months or more was 18.8 months (95% CI 17.2 to 20.3 months), compared with 2.6 months (95% CI 2.0 to 5.9 months) in patients receiving gefitinib for less than 3 months (p 0.0001). The mean (95% CI) estimated time to death for Caucasian patients was 16.0 months (95% CI 14.3 to 17.7 months) and the mean (95% CI) for patients with other ethnicity was 16.5 months (95% CI 13.7 to 19.3 months).

The Cox regression model included time to death as the dependent variable and ethnicity, gender, age, stage (at diagnosis), and performance status as covariates. Ethnicity, gender and age group were not independently associated with time to death. Patients initially diagnosed with less advanced disease Stage I disease survived for longer than patients diagnosed with Stage IV disease (HR 0.12 [95%CI 0.02 to 0.86]). Patients with PS0, 1 or 2 survived longer than PS3 patients. No other statistically significant differences were observed.