Non-Interventional Study Report

Study Code	NIS-OGR-DUM-2010/1
Version	1.0
Date	2 November 2015

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): The REASON study

STUDY REPORT SUMMARY (ABSTRACT)

A 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): The REASON study

Study objectives

The primary objective of the study was to collect epidemiological data on EGFR mutation status (M+, 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).

The secondary objectives of the study were:

- To collect real-life clinical outcome data under real life clinical practice in all EGFR M+ patients up to disease progression [e.g., PFS, overall survival (OS), disease-control rate (DCR)].
- To collect real-life pharmacoeconomic data (resource use) associated with the diagnosis and treatment of EGFR M+ patients.
- To collect real-life data on first line treatment decisions in EGFR M+ and M-/Mx patients.
- To collect real-life data on second line treatment decisions in EGFR M+ patients.
- To collect safety and tolerability data in terms of overall incidence of adverse events in the real-world first line treatment setting in EGFR M+ patients; only safety data for patients treated with gefitinib over the study observation period were planned to be further analysed and presented in the context of this study.

Study design

This was a multicentre, prospective, observational non-interventional study (NIS) pertaining to the collection of data from a planned sample size of 600 patients with histologically confirmed stage IIIB/IV NSCLC with known EGFR mutation status (i.e. EGFR M+, EGFR M- or EGFR Mx) who met the study eligibility criteria. All necessary information for the purposes of this study was collected using a paper Case Report Form (pCRF). Patients were enrolled by 22-hospital based physicians practicing in regional centres and specializing in oncology or lung diseases with an interest in lung cancer.

For EGFR M- or EGFR Mx patients as well as for EGFR M+ patients wishing to participate in other interventional studies, participation was completed by Visit 1. For EGFR M+ patients who did not wish to participate in other interventional studies study participation ended one (1) year after the last patient was included into the study unless the patient wished to end his/her participation in the study earlier, the patient experienced disease progression or died, or was lost to follow-up.

Results

A total of 589 patients of Caucasian origin (575 of whom had histologically confirmed stage IIIB/IV NSCLC and a known EGFR mutation status) were enrolled in the study by 22 geographically diverse hospital-based oncologists or lung disease specialists in Greece, between October 2010 and December 2013; the end of the study observation period occurred in December 2014.

EGFR mutation status

The EGFR mutation status was positive in 15.7% (90/575) (95% CI: 12.7-18.6), negative in 80.3% (462/575) (95% CI: 77.1-83.6), and not evaluable (EGFR Mx) in the remaining 4.0% (23/575) (95% CI: 2.4-5.6) of the patient population. Among the EGFR M+ patients with available data, exon 19 was the most common site of the mutation (59.6%; 53/89), followed by exon 21 (29.2%; 26/89), exon 20 (11.2%; 10/89) and exon 18 (2.2%; 2/89).

Sociodemographic and clinico-pathological characteristics by EGFR mutation status

At enrolment, the overall population had a mean age of 65.0±10.0 years, 73.4% (422/575) were males, and 82.6% (475/575) were either current or former smokers. The majority (73.4%; 422/575) of the patients had at least one clinically relevant comorbid or past condition, whereas 88.3% (508/575) had an ECOG PS of '0' or '1' and the remaining 11.6% (67/575) of '2' or '3'. Mean age at enrolment did not statistically significantly differ between the EGRF M+ and EGFR M- subpopulations [64.6±11.6 and 65.2±9.7 years; p=0.231], while gender and smoking status demonstrated a statistically significantly different distribution. In particular, males comprised 43.3% (39/90) of the EGFR M+ vs. 79.2% (366/462) of the EGFR M- patients (p<0.001). Furthermore, while 45.6% (41/90) of the EGFR M+ patients were current or former smokers and 54.4% (49/90) were never smokers, the respective proportions among EGFR M- patients were 89.0% (411/462) and 11.0% (51/462) (p<0.001). The majority of both EGFR M+ (83.3%; 75/90) and EGFR M-patients (71.4%; 330/462) had at least one clinically relevant comorbid/past condition, and an ECOG PS of '0' or '1' [94.4% (85/90); and 87.4% (404/462), respectively].

The median age at NSCLC diagnosis for the overall study population was 65.0 years (range: 35.8-86.8), while the median time elapsed from diagnosis to study enrolment was 1.8 (range: 0.1-141.8) months. The majority of the patients were diagnosed with stage IV disease (73.0%; 420/575), 20.5% (118/575) with stage IIIB, 5.9% (34/575) at a lower stage, and for 0.5% (3/575) the stage was unknown. The most predominant histological type was adenocarcinoma (81.4%; 468/575), followed by squamous cell carcinoma (in 10.4%; 60/575). None of the aforementioned characteristics significantly differed between EGFR M+ and EGFR M- patients. Specifically, the median age at disease diagnosis was 64.5 (range: 35.8-83.8) and 65.2 (range: 37.4-86.8) years among EGFR M+ and M- patients, respectively; 78.9% (71/90) vs. 72.1% (333/462) were diagnosed with stage IV NSCLC; and 85.6% (77/90) of EGFR M+ vs. 80.3% (371/462) of EGFR M- patients were histologically classified as adenocarcinoma.

At the initial disease diagnosis, 74.6% (429/575) of the overall patient population had a mean of 1.4±0.7 metastatic sites, with bone (41.7%; 179/429) being the most prevalent site. Of the EGFR M+ and EGFR M-patients, 78.9% (71/90) and 74.0% (342/462) had a mean of 1.4±0.6 and 1.4±0.7 metastatic sites, respectively, with bone being the most common metastatic site among both subpopulations [47.9% (34/71) for EGFR M+; 40.0% (137/342) for EGFR M-].

Multivariate logistic regression analysis indicated that the probability of having EGFR mutations was significantly lower in male patients with a smoking history and non-adenocarcinoma (OR: 0.304; 95% CI: 0.214-0.432; p<0.001). According to the multiple

regression model, female gender and never smokers were demonstrated as positive predictors of EGFR mutation positivity; specifically, the odds of EGFR mutation positivity were significantly lower in males versus females (OR: 0.680; 95% CI: 0.511-0.905; p=0.008), and smokers versus non-smokers (OR: 0.396; 95% CI: 0.296-0.530; p<0.001), while no statistically significant difference in the odds was detected for non-adenocarcinoma versus adenocarcinoma histology (OR: 0.946; 95% CI: 0.671-1.334; p=0.751).

Real-world treatment patterns

- In the *EGFR M+ population*, first line treatment was mainly comprised of EGFR-TKI monotherapy (64.8%; 57/88), followed by multi-agent chemotherapy (20.5%; 18/88), chemotherapy plus anti-VEGF antibody (10.2%; 9/88), mono-chemotherapy (2.3%; 2/88), and EGFR-TKI in combination with anti-VEGF antibody with/without chemotherapy (2.3%; 2/88); the three most commonly prescribed agents were gefitinib (47.7%; 42/88), carboplatin (28.4%; 25/88) and erlotinib (19.3%; 17/88).
- In the *EGFR M- patients*, first line therapy was mainly comprised of multi-agent chemotherapy (61.7%; 280/454), followed by chemotherapy plus anti-VEGF antibody (27.5%; 125/454), mono-chemotherapy (8.8%; 40/454), EGFR-TKI monotherapy (1.5%; 7/454) and anti-VEGF antibody only (0.2%; 1/454); the three most commonly prescribed agents were carboplatin (64.5%; 293/454), pemetrexed (39.0%; (177/454) and bevacizumab (27.8%; 126/454).
- In the *EGFR Mx patients*, first line therapy was mainly comprised of multi-agent chemotherapy (86.4%; (19/22), followed by chemotherapy plus anti-VEGF antibody (9.1%; 2/22), and mono-chemotherapy (4.5%; 1/22); the three most commonly prescribed agents were carboplatin (59.1%; 13/22), pemetrexed (54.5%; 12/22) and cisplatin (36.4%; 8/22).

Clinical outcomes in EGFR M+ patients

The EGFR M+ patients were exposed a median of 8.8 months (range: 0.5-42.2 months) to first line therapy as of the date of treatment onset. The median exposure to first line treatment among patients receiving 'chemotherapy only' was 5.1 (range: 1.1-31.8) months, for patients receiving 'EGFR-TKI only' was 9.7 (range: 0.5-42.2) months, and for patients receiving combination of anti-VEGF antibody treatment with chemotherapy and/or EGFR-TKI was 4.6 (range: 1.4-14.5) months.

During the study observation period, the DCR among the overall EGFR M+ population with available clinical response data (n=80) was 67.5% (95% CI: 57.2-77.8). In particular, the DCR was 72.2% (95% CI: 46.5-90.3) among patients receiving chemotherapy only (n=18), 71.2% (95% CI: 56.9-82.9) among those receiving EGFR-TKI monotherapy (n=52), and 40.0% (95% CI: 12.2-73.8) among those receiving combination of anti-VEGF antibody treatment with chemotherapy and/or EGFR-TKI.

The estimated median PFS was 13.2 months (95% CI: 3.7-19.4) in the subpopulation treated with chemotherapy only, 9.7 months (95% CI: 7.9-11.8) in those treated with EGFR-TKI monotherapy, and 4.7 months (95% CI: 1.4-8.4) in those treated with combination of anti-VEGF antibody treatment with chemotherapy and/or EGFR-TKI.

During the study observation period, a total of 12 deaths were recorded [13.6% (12/88) of the overall EGFR M+ population; 14.0% (8/57) among those treated with EGFR-TKI only, 5.0% (1/20) among those on chemotherapy only, and 27.3% (3/11) among those treated with combination of anti-VEGF antibody treatment with chemotherapy and/or EGFR-TKI].

Resource utilisation among the EGFR M+ population from diagnosis to study enrolment

From initial NSCLC diagnosis until study enrolment 46.7% (42/90) of the EGFR M+ patients, had been hospitalised at least once, corresponding to an all-cause hospitalization incidence rate of 2.50 hospitalisations per person-year.

Accordingly, 32.2% (29/90) of the EGFR M+ patients had performed outpatient visits with an all-cause outpatient visit incidence rate of 2.19 visits per person-year.

Post-enrolment resource utilisation among the EGFR M+ population

Over the post-enrolment study observation period (median: 6.9 months; range: 0.03-43.7 months), 39.0% (32/82) of the EGFR M+ patients had been hospitalized at least once (all-cause hospitalisation rate: 1.39 per person-year), 61.0% (50/82) had performed outpatient visits (all-cause outpatient visit rate: 3.32 per patient-year), 92.7% (76/82) had undergone imaging scanning, 9.8% (8/82) had received radiotherapy, and 84.1% (69/82) had received at least one concomitant medication with corticosteroids (29.5%; 26/88) and antiemetics (28.4%; 25/88) being the most frequently prescribed.

Among patients treated with chemotherapy only, EGFR-TKI monotherapy, and combination of anti-VEGF antibody treatment with chemotherapy and/or EGFR-TKI, the proportions of patients hospitalised were: 35.0%, 33.3% and 54.5%; the relevant hospitalisation rates were: 4.22, 1.17 and 3.34 hospitalisations per person year; the proportions of patients attending outpatient clinics were: 65.0%, 52.6% and 63.6%; and the outpatient visit rates were: 9.10, 3.04 and 7.06 visits per patient-year, respectively.

Safety data among the EGFR M+ population

Overall, 84 adverse events have been recorded for 36 patients (36/90; 40.0%) during the study observation period.

In regards to the gefitinib-treated population, 15.4% (8/52) of the patients experienced 14 NSADRs. The NSADRs by MedDRA PT reported with a frequency equal to or greater than 2.0% were ‘rash’ [7 events by 5/52 (9.6%) patients] and ‘acne’ [2 events by 2/52 (3.8%) patients]. Of the 14 NSADRs, 57.1% (8/14) were of mild intensity, 35.7% (5/14) of moderate and a single event (7.1%; 1/14) of severe intensity; 50.0% (7/14) of the events necessitated administration of additional treatment, 42.9% (6/14) did not require any action, while a single event (7.1%; 1/14) led to treatment discontinuation.

Among patients treated with gefitinib, only a single SADR was reported (1.9%); the SADR was ‘rash pruritic’, was of ‘mild’ intensity and necessitated ‘administration of additional treatment’.