Observational Study Report

Study Code	D7913C00074
Edition Number	1.0
Date	23-Mar-2017

A Diagnostic Study to Determine the Prevalence of EGFR Mutations in Asian and Russian Patients with Advanced NSCLC of Adenocarcinoma and Non-Adenocarcinoma Histologies: The IGNITE Study

China M+ Subgroup Real World Study Extension (Final Analysis)

Study dates:	First subject enrolled: 04-Apr-2014 Last subject last visit: 20-Jun-2016
Phase of development:	Not Applicable
National Co-ordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

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

STUDY REPORT SYNOPSIS

A Diagnostic Study to Determine the Prevalence of EGFR Mutations in Asian and Russian Patients with Advanced NSCLC of Adenocarcinoma and Non-Adenocarcinoma Histologies: The IGNITE Study

China M+ Subgroup Real World Study Extension (Final Analysis)

STUDY REPORT SUMMARY

SPONSOR: AstraZeneca AB, 151 85, Södertälje, Sweden

Developmental Phase: Not applicable

Study Completion Date: 20-Jun-2016

Date of Report: 23-Mar-2017 (Final, Version 1.0)

OBJECTIVES

The objectives of this extension to the IGNITE study were as follows:

- To record the overall survival (OS) and treatment sequences for subjects confirmed as epidermal growth factor receptor (EGFR) mutation positive (M+) via tissue/cytology.
- To evaluate the response and progression-free survival (PFS) of first-line and second-line therapy, and to evaluate quality of life (QoL) throughout the history of the disease.
- To summarise the progression patterns after first-line therapy.
- To determine the factors which impact the OS of EGFR M+ subjects in real-world settings (RWS).
- To record health care resource use for health economic evaluation.

METHODS

The IGNITE main study (AstraZeneca AB. Study D7913C00074) was an international, multicentre, cross-sectional, interventional diagnostic, and non-comparative study of EGFR mutation status in patients diagnosed with advanced non-small-cell lung carcinoma (locally advanced and/or metastatic disease) with both adenocarcinoma and non-adenocarcinoma histologies. A total of 3382 patients (including 1458 patients from China) were enrolled into the IGNITE main study over a 17-month period. The results were provided in a final report dated 12-January-2015.

The present document summarises data obtained during the RWS study extension for the IGNITE study over a 3-year follow-up period. This extension period only included those IGNITE main study subjects who were recruited in China with a confirmed EGFR tumour mutation (EGFR M+).

Inclusion Criteria

For inclusion in the IGNITE main study (and as a prerequisite for the IGNITE Extension study), patients fulfilled the following criteria:

1. Provision of informed consent before any study-specific procedures

2. Patients aged 18 years and older

3. Histological or cytological confirmed locally advanced non-small-cell lung carcinoma (stage IIIA/B) not suitable for curative treatment or metastatic (stage IV) non-small-cell lung carcinoma (NSCLC)

4. Newly diagnosed patients with locally advanced and/or metastatic NSCLC who were systemic-treatment naïve (ie, no chemotherapy or epithelial growth factor receptor-tyrosine kinase inhibitor [EGFR-TKI]) or patients with recurrent disease who previously received adjuvant chemotherapy (not including EGFR-TKI)

5. Provision of diagnostic cancer tissue or cytology sample upon inclusion (surgical specimen, biopsy sample, or cytology sample was acceptable)

6. Provision of a routine blood (plasma) sample in China, Russia, Taiwan, and Korea

The prescription of any medicinal product was clearly separated from the decision to include the patient in the study.

Exclusion Criteria

Patients could not enter the IGNITE main study (and as a prerequisite for the IGNITE Extension study), if any of the following exclusion criteria were fulfilled:

1. Involvement in the planning and/or conduct of the study (applied to both AZ staff and/or staff at the study site)

2. Previous enrolment in the present study

3. As judged by the investigator, any evidence of severe or uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)

4. Evidence of any other significant clinical disorder or laboratory finding that made it undesirable for the patient to participate in the study

5. Pregnant or breast-feeding

Patient Disposition

A total of 567 EGFR mutation positive subjects enrolled into the IGNITE main study in China. Of these, a total of 478 subjects were potentially available to participate in the RWS extension study at 18 participating sites. Of the 478 potential subjects, 80 (16.7%) died before RWS extension study initiation. The remaining 398 subjects (83.3%) were screened for the RWS extension. Of these, 212 subjects (53.3%) enrolled into the RWS follow-up extension (148 subjects before initiation and 64 subjects after initiation of the extension). The main reasons given for non-participation in the RWS extension study was that the subject is not willing to participate (136 subjects, 34.2%) or is not reachable (32 subjects, 8.0%).

Of the 212 subjects enrolled into the extension study, 207 subjects (97.6%) were judged evaluable and 5 subjects (2.4%) considered not evaluable. The primary reason for exclusion of 5 subjects from the evaluable group was non-completion of the main IGNITE study. In addition, a further 9 subjects were excluded from analysis because they had no first-line systemic cancer therapy identified at entry into the extension study. None of the 207 total subjects in the evaluable population completed the planned duration of the 3-year extension study because the study was terminated prematurely by the sponsor.

The principal reasons for subject discontinuation included study cancellation (87 subjects, 42.0%); death (86 subjects, 41.5%); lost to follow-up (23 subjects, 11.1%); and withdrew consent (11 subjects, 5.3%). There is no obvious difference in patient disposition based on the proportion of subjects recruited into the main IGNITE study before initiation of the RWS extension study compared with those subjects recruited after initiation of the RWS extension.

After each patient signed and dated the informed consent form on enrolment, patient demographics were recorded. The first-line therapy choice was noted for all patients. The second-line therapy choice was recorded following discontinuation of first-line therapy, where applicable. The protocol did not assign patients to a particular therapeutic strategy in advance. Medicinal products were used according to current practice and marketing authorisation. The study design did not include patient randomization into a control or reference treatment.

RESULTS

Demographics

Overall, the total evaluable population comprised 207 patients with a mean age (±standard deviation) of 58.6 (±10.4) years. Just over half of such evaluable patients are women (107 patients, 51.7%). All 207 evaluable patients (100.0%) are Asian.

There is no obvious imbalance in patient demographics (age, gender, or race) based on the proportion of subjects recruited into the main IGNITE study before initiation of the RWS extension study compared with those subjects recruited after initiation of the RWS extension.

Similar proportions of evaluable patients who had either not smoked or reported as current smokers with a World Health Organisation (WHO) performance status in the range of 0 to 3 were recruited into the main IGNITE study either before initiation of the RWS extension study compared with those patients recruited after initiation of the follow-up extension study.

Overall, the majority of patients were given their first NSCLC diagnosis at the time of entry into the extension study (189 patients, 91.3%). A minority of patients (18 patients, 8.7%) had an NSCLC diagnosis before study entry. Similar proportions of evaluable patients with a first NSCLC disease diagnosis at study entry were recruited into the main IGNITE study before initiation of the extension study (131 patients, 89.7%) compared with after initiation of the extension study (58 patients, 95.1%).

Among the histological types, overall 94.2% of patients had adenocarcinoma, and 5.8% had non-adenocarcinoma tumours. Patients were not reported in the "other" category. Overall, the most common (1% or more) adenocarcinoma type was "unknown" (166 patients, 87.8%), followed by solid (9 patients, 4.8%), acinar (6 patients, 3.2%), papillary (3 patients.1.6%), and mixed (4 patients, 2.1%).

Overall, the most common (1% or more) non-adenocarcinoma reported was squamous cell carcinoma (6 patients, 2.9%), and non-small cell carcinoma (5 patients, 2.4%). The pattern of tumour histological type and classification reported was similar in both subgroups of patients, including those who were recruited into the main IGNITE study before and those who were recruited after the follow-up extension study was initiated.

Overall, most patients (187 patients, 90.3%) had not received previous treatment before recruitment into the main IGNITE study either before initiation of the follow-up extension study (130 patients, 89.0%) or after initiation of the extension study (57 patients, 93.4%). For those patients that received previous lung cancer treatment (total of 20 patients, 9.7%), most were surgically treated (17 patients, 85%) in combination with either adjuvant chemotherapy (8 patients, 40%) or radiotherapy (3 patients, 15%).

No obvious imbalance is present in the proportion of patients with or without previous lung cancer treatment and recruited into the main IGNITE study either before initiation of the follow-up extension or after initiation of the extension study.

The EGFR mutation subtypes reported in the follow-up extension study included: Exon 18 (G719X mutation only); Exon 19 (Exon 19 deletion only; Exon 19 deletion + other; Exon 19 other only); Exon 20 (Exon 20 insertions only); Exon 21 (L858R mutation only; L858R mutation + other; L861Q mutation only) and several other tumour subtypes.

No obvious imbalance was noted in the proportion of patients in the most common EGFR mutation subtypes whether recruited into the main IGNITE study either before initiation of the follow-up extension study or after initiation of the extension study.

Study Variables

The study variables for this follow-up extension study are summarised in the table below:

Additive Variables for the China M+ Subgroup RWS

Overall survival	OS in the whole EGFR M+ population and different subgroups regarding different treatment strategy.
Systemic treatment sequences after testing	Name of treatment Treatment start and discontinuing date Reason for treatment choice (including clinical study enrolment) and discontinuing Drop-out rate of 1st and 2nd line
EGFR-TKI exposure time[a]	Type: gefitinib, erlotinib or icotinib (or other EGFR-TKI via clinical study) Mode: first line, maintenance or later line; re-challenge or treatment beyond progression (TBP); monotherapy or concurrent/ intercalating with chemotherapy
Tumour assessment	ORR, PFS
Progression patterns after 1st line	Type of progression: previously evaluated lesion / new lesions Focus of progression: solitary lesion / multiple lesions Progression sites: intracranial / systemic Patient status: asymptomatic / symptomatic
QoL	FACT-L questionnaire
WHO PS	Performance score
Health care resources use	Including inpatient hospital stays, outpatient visits, emergency room visits and major medical procedures
Factors which impact the OS	Including demographic factors, disease status, etc

Abbreviations: EGFR-TKI = epidermal growth factor receptor – tyrosine kinase inhibitor; FACT-L = functional assessment of cancer therapy - lung; M+ = mutation-positive; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = Quality of Life; TBP = treatment beyond progression; WHO PS = World Health Organisation – performance score

[a] EGFR-TKI exposure time: the time between first and last administration, including all the exposure periods

EFFICACY

Choice of Treatment

Overall, systemic anti-cancer treatment is the most common choice for first-line therapy (195 patients, 94.2%). The remaining evaluable patients (12 patients, 5.8%) were treated with either radiotherapy, surgery, or other treatment.

Of the patients treated with systemic anti-cancer agents (either alone or in combination), the 10 most common treatment regimens were Gefitinib only (30.4%); Icotinib only (10.1%); Cisplatin, Pemetrexed (9.2%); Cisplatin, Gemcitabine (7.2%); Carboplatin, Pemetrexed (6.8%); Other Chemotherapy (3.4%); Cisplatin, Paclitaxel (2.9%); Erlotinib only (2.9%); Carboplatin, Paclitaxel (2.4%); and Pemetrexed, Other Chemotherapy (2.4%). Similar proportions of evaluable patients provided with systemic anti-cancer treatment are found in the subgroup recruited into the main IGNITE study before initiation of the follow-up extension study compared with after initiation of the extension study.

Overall, systemic anti-cancer treatment remained the most common choice for second-line therapy (123 patients, 59.4%). However, first-line treatment remained ongoing for approximately 1/3rd of the evaluable patients (74 patients, 35.7%). The remaining patients were given other treatment alternatives (10 patients, 4.8%).

Of the evaluable patients treated with second-line systemic agents, the most common agents used were Pemetrexed (36.6%); Docetaxel (26.0%); Other Chemotherapy (23.6%); Gefitinib (21.1%); Cisplatin (20.3%); Carboplatin (20.3%); Icotinib (19.5%); Erlotinib (17.9%); Gemcitabine (14.6%); and Paclitaxel (6.5%) and Investigational Agent (5.7%). The remaining agents were chosen at a frequency less than 5%. Similar proportions of patients were treated with second-line systemic anti-cancer therapy in the cohort recruited into the main IGNITE study before initiation of the follow-up extension study compared with those recruited after initiation of the extension study.

Exposure to EGFR-TKI Treatment

Overall, the number and proportion of evaluable patients who received EGFR-TKI based treatment (154 patients, 74.4%) is larger compared with those patients who did not receive such treatment (53 patients, 25.6%). A larger number of evaluable patients received first-line EGFR-TKI treatment (92 patients, 44.4%) compared with patients given second-line or later EGFR-TKI treatment (76 patients, 36.7%).

The median number of exposure days [95% confidence interval (CI)] for evaluable patients given EGFR-TKI treatment is reported in the following order: Gefitinib (82 patients, 482 exposure days [357.0, 626.0]; Icotinib (44 patients, 376.5 exposure days [282.0, 483.0]); Erlotinib (28 patients, 349.5 exposure days [267.0, 463.0]); Other EGFR-TKI (6 patients, 287 exposure days [1.0, 506.0]); and Afatinib (1 patient, 98.0 exposure days).

Overall Survival (OS)

Clinically meaningful differences are noted in the OS for surviving evaluable patients by time of main study recruitment with respect to initiation of the follow-up extension study. The median overall OS for patients recruited into the main IGNITE study before initiation of the follow-up extension (141 patients) is not calculable (NC) (95% CI 27.8, NC). This result compares with a median OS of 23.1 months (95% CI 18.1, NC) for the treatment group (57 patients) recruited after initiation of the extension study.

This difference is, in part, related to the loss of 80 eligible patients who died before they had the opportunity to consent and enter the extension study (missed early deaths). The end result is a biased subset of patients whose survival time was greater than the time required to set up the study extension. The corresponding subset of patients who were recruited into the main IGNITE study after initiation of the extension study, and who reported with a median OS of 23.1 months, may be a less biased sample.

The median OS for evaluable patients given any EGFR-TKI treatment regimen (30.6 months; 95% CI 25.4, NC) is similar to that observed in the patient group that did not receive EGFR treatment (NC, 21.2, NC). The Kaplan-Meier survival plots are similar and overlap considerably for the EGFR-TKI treatment subset (152 patients) compared with the no EGFR-TKI treatment subset (46 patients). However, it is difficult to make valid comparisons because the treatment groups were not randomly assigned.

Following inspection of the preliminary results obtained at the interim analysis (02-June-2015), a decision was taken to prematurely discontinue the extension study, in part because some aspects of the study design had the potential to bias the results for some of the planned analyses, including those objectives that impacted OS and measures used to determine tumour response. This bias was driven by the fact that potential survival duration is itself dependent on when a subject was recruited into the main IGNITE study relative to the extension study initiation, and the necessary exclusion of those subjects who had died before that date.

Objective Response Rate (ORR)

The overall ORR for first-line treatment was 33.8% (95% CI 27.4, 40.7). The systemic anti-cancer treatments that provided ORR scores in 10 or more patients are as follows: Gefitinib (63 patients, 34.9%); Cisplatin (48 patients, 35.4%); Pemetrexed (43 patients, 23.3%); Carboplatin (26 patients, 23.1%); Gemcitabine (24 patients, 45.8%); Icotinib (21 patients, 33.3%); and Paclitaxel (14 patients, 21.4%). Radiotherapy (3 patients, 66.7%) and Surgery (1 patient, 0%) is employed less often as first-line therapy.

The systemic anti-cancer treatments that provide ORR scores for second-line treatment in 10 or more patients are as follows: Pemetrexed (45 patients, 28.9%); Docetaxel (32 patients, 40.6%); Other Chemotherapy (29 patients, 31.0%); Gefitinib (26 patients, 38.5%); Carboplatin (25 patients, 36.0%); Cisplatin (25 patients, 36.0%); Icotinib (24 patients, 45.8%); Erlotinib (22 patients, 45.5%)and Gemcitabine (18 patients, 33.3%). However, these data

should be viewed with caution because the responses from some patients may have been obtained before the second line treatment was given (ie response at any time).

Progression-Free Survival (PFS)

Overall, 30.4% (63 patients) did not report a progression event. Response evaluation criteria in solid tumours (RECIST) defined progressive disease is noted in 36.7% (76 patients), and death observed in 19.3 % (40 patients) during the course of the study. A total of 9.2% of patients were noted as lost to follow up, and 4.3% (9 patients) had no first-line treatment reported. Overall, the median progression-free survival time is 18.1 months (95% CI 15.2, 21.4).

PFS data is reported for evaluable patients that received first-line treatment with EGFR-TKI therapy in 92 patients. RECIST defined progressive disease is reported in 42.4% (39 patients), and death in 20.7% (19 patients) during the course of the study. Similar PFS findings were also made in evaluable patients treated with other (non-EGFR-TKI) first-line regimens. The median survival time was 16.7 months for evaluable patients receiving first-line EGFR-TKI treatment and 21.4 months for patients given other (non-EGFR-TKI) first-line therapy. Note that it is difficult to make valid comparisons because the treatment groups were not randomly assigned.

Tumour Progression Pattern

Overall, tumour progression is observed after the start of first-line treatment in 38.4% (76 patients) of those with first line treatment reported. Of the 76 tumour progressions identified, 67.1% (51 patients) are previously evaluated lesions, and the remainder (32.9%, 25 patients) classed as new lesions. The focus of expression is evenly divided between solitary lesions (51.3%, 39 patients) and multiple lesions (47.4%, 36 patients). Progression sites are mostly systemic (88.2%, 67 patients) and reported as asymptomatic (46.1%, 35 patients), symptomatic (48.7%, 37 patients) or unknown (5.3%, 4 patients). The tumour progression pattern reported after the start of first-line treatment for the patient population given EGFR-TKI therapy is qualitatively similar to that observed in the patient group not provided with EGFR-TKI treatment.

Quality of Life (QoL) FACT-L

Overall, the median Functional Assessment of Cancer Therapy - Lung (FACT-L) reported total score (range) increased from 93.0 (63.0, 126.7) at Visit 3 (Day 90) to 105.0 (52.5, 131.9) at Visit 9 (21 Months) and then decreased to 88.6 (65.9, 92.7) at Visit 14 (36 Months). This U-shaped response may reflect an initial improvement in patient QoL with assigned anti-cancer systemic treatment followed by a later decline as either the disease progresses, the side effects of the therapy become less tolerable, or the total number of patients remaining in the study decrease significantly. Review of the FACT-L data obtained for EGFR-TKI compared with non-EGFR-TKI treatment of the evaluable patient population shows a similar pattern of response in both treatment groups. A numerical improvement in patient reported QoL from Visit 3 (Day 90) is largely sustained through Visit 12 (30 months), after which a

decrease in FACT-L score is noted as the disease progresses or the number of patients remaining in the study decreases substantially.

Quality of Life (QoL) WHO Performance

Overall, the QoL WHO performance status of the evaluable patient population decreases progressively over the course of the study. At early time points (Visit 1 [Day 1] through Visit 3 [6 Months]), the number of patients with a WHO performance score (PS) of 0 is similar to those patients observed with a WHO score of 1. As the study continued, there is a gradual shift towards WHO PS of 1 or more and a corresponding increase in the proportion of patients reported as "worsened" in terms of change in performance status compared to entry into the main IGNITE study. Review of the WHO performance status scores obtained in the EGFR-TKI treated compared with the non-EGFR-TKI treated patient subgroup did not show any obvious trend(s) or clinically meaningful difference(s) in response. As the study progressed, similar shifts towards higher WHO PS are noted along with an increase in the proportion of patients reporting as "worsened".

Health Care Resource (HCR) Use

Overall, Health Care Resource (HCR) use is reasonably constant over the course of the study (patients using health care resources range: 84.6% to 94.7%) in the evaluable population. However, the median number of hospital days (min, max) is higher (14.0 days, 1.0, 87.0) at Visit 3 (Day 90) compared with any subsequent visit (Visits 4 to 14, median ranges from 3.0. to 9.0 days). Similarly, the proportion of major medical procedures reported at Visit 3 (25.1%) is higher compared with any subsequent study visit (Visits 4 through 14, range 0.0% to 8.8%). There is a large decrease in the number of evaluable patients remaining in the study after Visit 12 (30 Months). This, in part, is related to the decision by the sponsor to terminate the study early.

Qualitatively similar findings are obtained when the early visit HCR data is reviewed in relation to EGFR-TKI use compared to HCR data collected in patients given non-EGFR-TKI therapy, both showing a reduction in median number of hospital days after Visit 3. There are some quantitative differences in HCR data between the two EGFR-TKI subgroups. The evaluable patient subgroup receiving EGFR-TKI treatment reports the proportion of major medical procedures at 12.8% on Visit 3 and the median number of hospital days as 10.0 (range 1.0 to 57.0 days). In the patient subgroup that is not treated with an EGFR-TKI regimen, the corresponding HCR data at Visit 3 is larger for both major medical procedures (38.8%) and the median number of hospital days (20.5 days, range 2.0, 87.0). The medical significance of this quantitative difference in subgroup HCR score at Visit 3 (day 90) is unclear.

EFFICACY SUMMARY

- There is no obvious overall imbalance in patient demographics, tumour histology type, NSCLC diagnosis, smoking history, WHO performance status, previous lung cancer treatment, or EGFR mutation subtype frequency based on the proportion of subjects

recruited into the main IGNITE study either before initiation of the RWS extension study compared with after initiation of the extension study.

- In the patient group who received EGFR-TKI as first line treatment, there were more females, older patients, non-smokers, with poorer PS, and who were more likely to have several organs with metastases.
- Overall, systemic anti-cancer treatment is the most common choice for both first-line and second-line therapy of patients in this RWS extension study.
- Of the patients treated with systemic anti-cancer agents (either alone or in combination), the 5 most common treatment regimens were Gefitinib only; Icotinib only; Cisplatin, Pemetrexed; Cisplatin, Gemcitabine; and Carboplatin, Pemetrexed.
- Clinically meaningful differences are noted in the OS for surviving evaluable patients who were recruited into the main IGNITE study before the follow-up extension study compared to the patient subgroup recruited after initiation of the extension study.
    - The observed difference in OS for the patient subgroup recruited before initiation of the follow-up extension study is, in part, related to the loss of eligible patients who died before they had the opportunity to consent and enter the extension study.
    - The end result of these missed early deaths is a biased subset of patients whose survival time was greater than the time required to set up the study extension.
    - The corresponding subset of patients who were recruited into the main IGNITE study after initiation of the extension study, may be a less biased sample.
- No medically important imbalance was observed in evaluable patient response to EGFR-TKI treatment compared with non-EGFR-TKI therapy using the parameters of OS, ORR, PFS, or tumour progression pattern(s).
- QoL measures (FACT-L and WHO performance status) obtained in the evaluable patient population did not show any consistent pattern of response.

SAFETY

No safety data were collected in this RWS, non-interventional, follow-up extension study.

CONCLUSIONS

- Overall, systemic anti-cancer treatment is the most common choice for both first-line and second-line therapy of patients in this RWS extension study.
- Of the patients treated with systemic anti-cancer agents (either alone or in combination), the 5 most common treatment regimens were Gefitinib only; Icotinib only; Cisplatin, Pemetrexed; Cisplatin, Gemcitabine; and Carboplatin, Pemetrexed.
- Clinically meaningful differences are noted in the OS for surviving evaluable patients who were recruited into the main IGNITE study before the follow-up extension study compared to the patient subgroup recruited after initiation of the extension study.

  - The observed difference in OS for the patient subgroup recruited before initiation of the follow-up extension study is, in part, related to the loss of eligible patients who died before they had the opportunity to consent and enter the extension study.
  - The end result of these missed early deaths is a biased subset of patients whose survival time was greater than the time required to set up the study extension. The corresponding subset of patients who were recruited into the main IGNITE study after initiation of the extension study, may be a less biased sample.
- Following inspection of the preliminary results obtained at the interim analysis (02-June-2015), a decision was taken to prematurely discontinue the extension study.
- This decision by the sponsor was made, in part, because aspects of the study design had the potential to bias the results for some of the planned analyses, including those objectives that impacted OS and measures used to determine tumour response.