CLINICAL STUDY REPORT

A Prospective, Non-interventional Evaluation of Symptoms Improvement of First-Line Therapy of EGFR Tyrosine Kinase Inhibitor in Advanced NSCLC Patients with Positive EGFR mutation – the SMILE study

PROTOCOL NO.	**NIS-OTW-ATC-2013/1**
DEVELOPMENT PHASE	**Phase IV**
REPORT VERSION	**v1.0**
SPONSOR	**AstraZeneca**
ISSUED BY	**Formosa Biomedical Technology Corp., CRO**
DATE	**Sep-20-2016**

AMENDMENTS

No.	Date
1	N/A
2	N/A
3	N/A

1 TITLE PAGE

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DEVELOPMENT PHASE	Phase IV
INVESTIGATIONAL DRUG	EGFR Tyrosine Kinase Inhibitor
INDICATION	Advanced NSCLC with positive EGFR mutation
FIRST ENROLLMENT	Nov-07-2013
LAST COMPLETED	Sep-22-2015
PRINCIPAL INVESTIGATOR(S)	[redacted]
SPONSOR	AstraZeneca 21st Fl., 207, Tun-Hwa South Rd., Sec. 2, Taipei Metro Building, Taipei 10602, Taiwan

DATE OF REPORT Sep-20-2016

COMPLIANCE**:** The study was performed in compliance with the Good Clinical Practice (GCP). ***CONFIDENTIALITY***: The information contained in this report is confidential and is intended for the use of clinical investigators. The protocol and report are the property of AstraZeneca and should not be copied by, distributed to persons not involved in this clinical trial, or published without the permission of AstraZeneca.

2 SYNOPSIS

PROTOCOL NO.: NIS-OTW-ATC-2013/1	**INVESTIGATIONAL PRODUCT:**
SPONSOR: AstraZeneca	**EGFR Tyrosine Kinase Inhibitor**

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CO- INVESTIGATOR(S)	[redacted]

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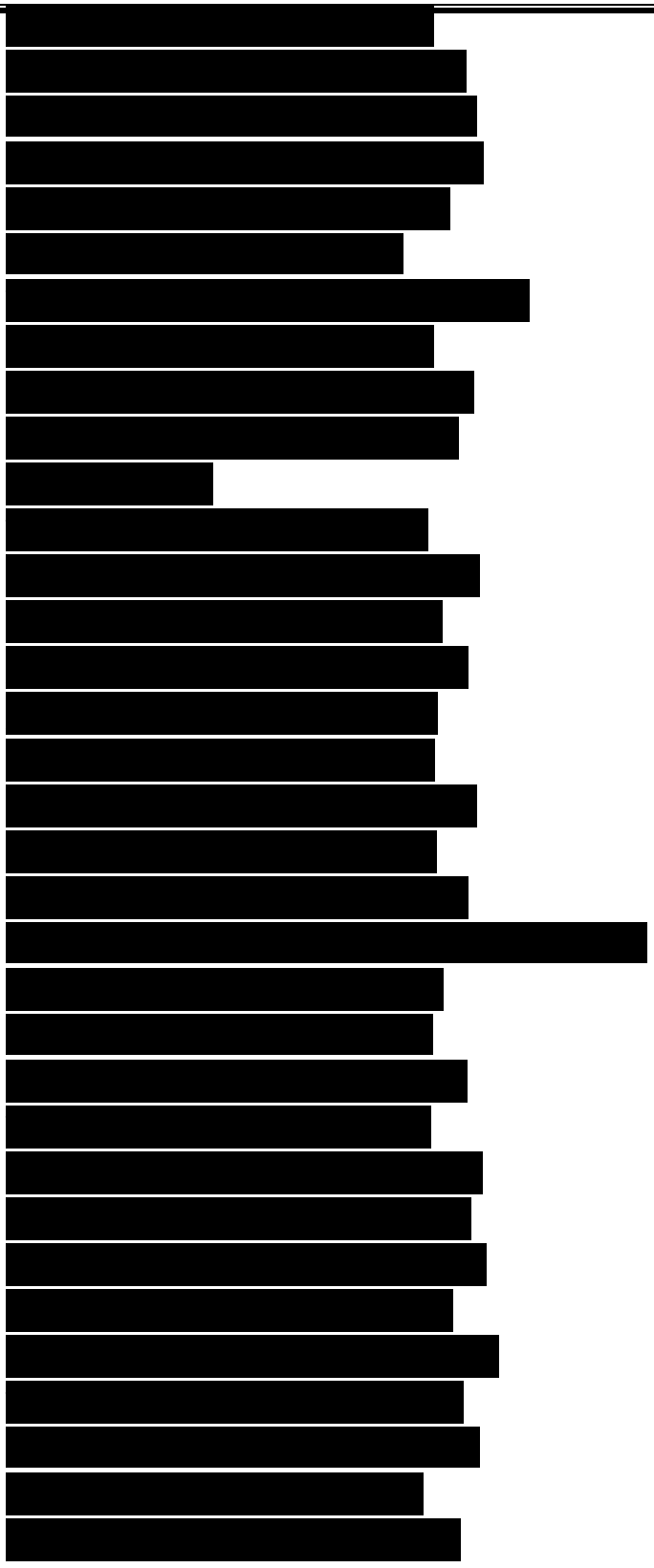

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[redacted]

STUDY CENTER(S)	11 hospitals
STUDY PERIOD	Date of first enrollment: Nov-07-2013 Date of last completed: Sep-22-2015
OBJECTIVES	**Primary Objective** To estimate symptom improvement rates in patients with locally advanced or metastatic NSCLC and positive EGFR mutation who received EGFR-TKIs as the first-line treatment. A clinically meaningful improvement was

defined as an increase from baseline of 2 or more points for LCS (Lung Cancer Scales) at Week 4.

Secondary Objectives

1. To estimate symptom improvement rates at Week 2 and 12
2. To estimate mean change from baseline in overall QoL scores using the FACT-L instrument and LCS score at Week 2, 4, and 12.
3. To estimate the proportion of patients exhibiting an LCS change of 7 points or more at Week 2, 4, and 12.
4. Subgroup information of symptom improvement rate, QoL and disease-related symptom scores by gender, smoking status, smoking pattern, WHO performance, number of metastatic sites, female/never smokers, and patients with COPD at Week 2, Week 4, and Week 12.

METHODOLOGY This was an open-label, non-interventional, single-arm, multicenter study

NUMBER OF PATIENTS Around 400 subjects were planned to enroll from 10 sites in Taiwan. Finally, 346 patients were enrolled, with 298 eligible patients participated in this study and 43 patients discontinued the study.

INVESTIGATIONAL PRODUCT Gefitinib 250 mg oral once daily or erlotinib 150 mg oral once daily following real-world setting

REFERENCE THERAPY Not applicable for this single-arm study

DURATION OF TREATMENT Prospectively followed for a 12-week period

ELIGIBILITY CRITERIA

The target population was patients with locally advanced or metastatic NSCLC, positive EGFR mutation and administration with EGFR-TKIs.

Inclusion Criteria

The subject population that was observed in the NIS, must fulfill all of the following criteria:

1. Provision of informed consent form.
2. Female and male aged 20 years and older.
3. Patients diagnosed with symptomatic, locally advanced or metastatic (stage IIIb/IV) NSCLC.
4. Patients who were confirmed positive for EGFR mutation which was genotyped in certificated laboratories.
5. Patients with a prescription of EGFR-TKI as their first-line treatment but had not started treatment.
6. Patients who were able to complete the questionnaires.
7. The prescription of the medicinal product was clearly separated from the decision to include the subject in the NIS.

Exclusion Criteria

Involvement in any planning and/or conduct of the clinical trial.

Criteria for Discontinuation

Subjects might discontinue from the NIS at any time. Specific reasons for discontinuing a subject from this NIS

were:

1. Voluntary discontinuation by the subject, who his/her participation in the NIS at any time, without prejudice to further treatment.
2. Incorrect enrollment (inclusion/exclusion criteria were not fulfilled).
3. EGFR Mutation wild type patients: If patients had entered study before their EGFR status had been known and in the event that the result of the test showed EGFR wild type, they were withdrawn from this study; any LCS data captured up to this point was discarded.

ENDPOINTS

Primary Endpoint

The primary endpoint was the proportion of patients demonstrating a clinically meaningful improvement post 4 weeks of EGFR-TKI therapy defined as an increase in LCS ≥ 2 points from baseline.

Secondary Endpoints

1. The proportion of patients demonstrating a clinically meaningful improvement post 2 weeks and 12 weeks of EGFR-TKI therapy as defined as an increase in LCS ≥ 2 points from baseline.
2. Mean change from baseline to Week 2, 4, and 12 in FACT-L, TOI, and LCS.
3. The proportion of patients demonstrating a clinically meaningful improvement post 2, 4, and 12 weeks of EGFR-TKI therapy as defined as an increase in LCS ≥ 7 points from baseline.
4. Descriptive statistics of symptom improvement rate

(defined as LCS ≥ 2 points changed from baseline), QoL and disease-related symptom scores at Week 2,4, and 12 and summarized by the following factors:

a. gender (male and female)

b. smoking status (never smoked, ex-smoker, occasional smoker and regular smoker)

c. smoking pattern by pack-year (0, >0-10, >10-20, >20-30, >30-40, >40-50, >50)

d. WHO performance status (0, 1, 2, 3-4)

e. number of metastatic sites (0, 1, 2, ≥3)

f. female/never smokers

g. patients with COPD

STATISTICAL METHODS

All efficacy analyses were performed using the evaluable-for-symptom improvement (EFS) population. The clinical improvement rate of LCS-assessed symptom was summarized at all post-baseline visits with 95% exact confidence interval during study. The mean change from baseline of QoL and LCS score was analyzed using paired t-test.

For categorical variables, summary statistics included the number of subjects and percentage for each category. For continuous variables, summary statistics included the number of observations, mean, standard deviation, median, minimum, and maximum values.

RESULTS

BASELINE CHARACTERISTICS

A total of 286 patients composed the EFS population. The

average age was 65.1 ± 12.45 years old, ranging from 31.1 to 90.4 years. More females were enrolled (female vs. male: 62.6% vs. 37.4%). Most of them (74.0%) were non-smokers, 14.7% were ex-smokers, and 11.3% were smokers. At the time of study inclusion, the majority of patients (88.8%) harbored stage IV NSCLC, and the remaining 9.1% of patients harbored stage III NSCLC. Most patients (88.5%) had metastatic disease.

At the beginning, 72.4% of patients were treated with Gefitinib, 18.9% received Erlotinib, and 8.7% took Afatinib. During the study period, no patients changed medication, and almost all patients (>95%) stayed at the same dosing level. Only 1.0% to 2.6% of patients receiving Gefitinib, 3.7% to 4.7% of patients receiving Erlotinib, and 4.2% of patient receiving Afatinib had changed the dose.

PRIMARY ENDPOINT

At Week 4, 43.4% of patients achieved clinically meaningful improvement of LCS ≥ 2 points, while 34.5% of patients had no significant changes (change in LCS between -2 and 2 points) and 22.0% of patients became worse (decrease in LCS ≥ 2 points).

SECONDARY ENDPOINTS

I. Clinically meaningful improvement (LCS ≥ 2) at Week 2 and Week 12

Improvement rate was sustained from Week 2 to Week 12. At Week 2, 45.8% of patients showed clinically meaningful improvement; while at Week 12, 44.1% of patients demonstrated clinically meaningful improvement.

II. Mean change in FACT-L, TOI, and LCS

Improvement in 3 scales showed early at Week 2 and maintained until Week 4 and Week 12. However, the average increment in FACT-L, TOI, and LCS might not be clinically meaningful*.

*Clinically meaningful change: FACT-L, 6 points; TOI, 6 points; LCS, 2 points

For FACT-L, the total score was increased by 4.0 to 4.9. For TOI, increases were observed up to 2.4 to 3.1. For LCS, it was slightly increased by 1.7 to 2.0.

III. Clinically meaningful improvement (LCS ≥ 7)

At Week 2, 15.0% of patients achieved clinically meaningful improvement of LCS ≥ 7. Improvement rate was slightly increased to 18.9% at Week 4 and 16.4% at Week 12.

IV. Subgroup analysis of clinically meaningful improvement (LCS ≥ 2), QoL, and disease-related symptom scores

Clinically meaningful improvement rate (LCS ≥ 2)	
Characteristics	**Findings**
Gender	Comparable
Smoking	Comparable
Smoking pattern	- Higher: Population of >0-10 pack-years (54.5% to 72.7%) & Population of > 20-30 packs-year (57.1% to 64.3%)

	- Lowest: Population of >40-50 packs-year (28.6%)
Metastatic sites	- Higher: Population with more metastatic sites (2 sites: 51.6% to 57.8%, ≥ 3 sites: 50.0% to 76.9%) - Lower: Population with 0 or 1 metastatic site (35.5% to 48.4% and 35.8% to 41.8%, respectively)
COPD	- Without COPD: sustained improvement rate (42.9% to 45.1%) - With COPD: decreasing improvement rate (from 61.5% to 30.8%) - Need more evidence for subgroup comparison (imbalanced population)
WHO performance status	- No remarkable difference was observed among subgroups - Slightly higher in WHO performance status 1 (49.5% to 54.3%)
EFGR-TKI therapy	Improvement rate was comparable between different EGFR-TKI therapies (around 40% to 50%).
Summary	- Gender, COPD status, and WHO performance status might have no significant impact on improvement rate of patient reported LCS.

	- Smoking might have negative impact on LCS. - Patients with more metastatic sites reported higher improvement rate (need more evidence).

Change in LCS score (Clinically meaningful: Change in LCS ≥ 2 points)	
Characteristics	**Findings**
Gender	Increment observed in male patients was clinically meaningful, but that of females was not. (Male vs. Female: 2.0 to 2.3 vs. 1.4 to 1.9).
Smoking	Ex-smokers demonstrated clinically meaningful improvement with change of 2.7 to 3.1. Changes in smokers were small and not clinically significant (0.9 to 1.8).
Smoking pattern	- Patients who smoked less than 30 packs per year showed a higher increment in LCS with clinical significance. - Most of the changes in patients smoking more than 30 packs per year were small and not clinically meaningful.
Metastatic sites	- Patients with at least 2 metastatic sites showed meaningful improvement.

		- Patients with less than 1 metastatic site showed smaller and meaningless change.
	COPD	- Increment in LCS score in patients with COPD was clinically meaningful and higher than that of patients without COPD. - Need more evidence for subgroup comparison (imbalanced population)
	WHO performance status	- Meaningful improvement exhibited in patients of WHO performance status 1 (2.4 to 2.7). - Changes observed in population of WHO performance status 0, 2, and 3-4 were small and not clinically meaningful.
	EGFR-TKI therapy	- Clinically meaningful change in LCS score was observed in patients treated with Gefitinib. - Changes observed in patients receiving Erlotinib and Afatinib were small and mostly not clinically meaningful.
	Summary	- Male patients showed better outcome. - Smoking and higher WHO performance status score might have negative impact on patient reported LCS score. - Increase in LCS score seemed to be higher in patients with more

	metastatic sites (need more evidence). - Improvement was observed in patients receiving Gefitinib.

Change in TOI score (Clinically meaningful: Change in TOI ≥ 6 points)	
Characteristics	**Findings**
Gender	No clinically meaningful change was observed in both male and female groups.
Smoking	Most of the changes were not clinically meaningful. Only ex-smokers showed a meaningful change of 6.0 ± 16.30 at Week 4.
Smoking pattern	- Meaningful improvement was only observed at Week 4 in patients smoking less than 10 packs per year (8.9 ± 18.34). - Changes in other group were smaller and without clinical meaning.
Metastatic sites	- Patients with at least 3 metastatic sites showed clinically meaningful improvement (7.3 to 10.6). - Changes in other population were smaller and without clinical meaning.
COPD	- No clinically meaningful change was observed in both patients

	with COPD and patients without COPD. - Need more evidence for subgroup comparison (imbalanced population)
WHO performance status	- No clinically meaningful change was observed in all the subgroups. - Population of WHO performance status 3-4 showed reduction in TOI score (-3.8 to -2.1), but had no clinical meaning.
EGFR-TKI therapy	- No clinically meaningful change was observed in all the subgroups. - Gefitinib treatment demonstrated the highest increase from baseline, but had no clinical meaning.
Summary	- Smoking and higher WHO performance status score might have negative impact on patient reported TOI score. - Increase in TOI score seemed to be higher in patients with more metastatic sites (need more evidence).

Change in FACT-L score **(Clinically meaningful: Change in FACT-L≥6 points)**	
Characteristics	**Findings**

	Gender	Increment observed in male patients was clinically meaningful, but that of females was not (Male vs. Female: 4.9 to 6.5 vs. 2.9 to 4.0).
	Smoking	- Clinically meaningful improvements were observed in ex-smokers at Week 4 (6.8 ± 17.24) and smokers at Week 12 (7.7 ± 32.01). - The change in non-smokers showed no clinical significance (3.0 to 3.9).
	Smoking pattern	- Meaningful improvement was noted in population smoking less than 10 packs-year, more than 20 to 30 packs-year, more than 30 to 40 packs-year, and more than 40 to 50 packs-year. - Changes in population smoking more than 10 to 20 packs-year and more than 50 packs-year were small and without clinical meaning
	Metastatic sites	- Patients with at least 2 metastatic sites showed greater improvement than patients with no metastasis or 1 metastatic site did. - Patients with 2 and at least 3 metastatic sites showed clinically meaningful improvement (2

		sites: 3.6 to 6.2, ≥ 3 sites: 10.0 to 14.9). - Changes in patients with no metastasis or 1 metastatic site were smaller and without clinical meaning.
	COPD	- No clinically meaningful change was observed in both patients with COPD and patients without COPD. - Need more evidence for subgroup comparison (imbalanced population)
	WHO performance status	- Populations of WHO performance status 1 and 2 showed clinically meaningful improvement at Week 4 (6.2 ± 20.55) and Week 2 (6.2 ± 20.90), respectively. - Increments in populations of WHO performance status 1 were generally higher. - A clinically meaningful exacerbation was noted in opulations of WHO performance status 3 and 4 at Week 12 (-7.5 ± 17.29).
	EGFR-TKI therapy	- Clinically meaningful improvement was observed in patients treated with Gefitinib at Week 4 (6.6 ± 18.50).

		- Changes in the Gefitinib group were higher than the Erlotinib and Afatinib group, with significant and clinically meaningful difference between groups (P=0.026 at Week 2 and P=0.035 at Week 4). - Changes observed in patients receiving Erlotinib and Afatinib were small and not clinically meaningful.
	Summary	- Male patients showed better outcome. - Higher WHO performance status score might have negative impact on patient reported FACT-L score. - Increase in FACT-L score seemed to be higher in patients with more metastatic sites (need more evidence). - Improvement was observed in patients receiving Gefitinib.

CONCLUSION [redacted]

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