Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

1. ABSTRACT

Name of company:		Nippon Boehringer Ingelheim Co., Ltd.	
Name of finished medicinal product:		Giotrif®	
Name of active ingredient:		Afatinib (ATC code: L01XE13) Antineoplastic agents Tyrosine kinase inhibitors	
Report date: 24 Sep 2024	**Study number:** 1200-0322	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	J-REGISTER: Japanese REal-world data for treatment of afatinib (GIotrif®) in first-line setting and Subsequent Therapies for patients with advanced epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma.		
Keywords:	Afatinib (Giotrif®); epidermal growth factor receptor mutation (EGFR mutation); tyrosine kinase inhibitors; time on treatment (TOT); first-line; non-small cell lung cancer (NSCLC); real-world data		
Rationale and background:	Afatinib was commercialized on 7 May 2014 in Japan for treatment of patients with metastatic NSCLC whose tumors have activating EGFR mutations. There is a scarcity of information regarding afatinib treatment in first-line setting, such as proportion of acquired resistance of T790M mutation, treatment status of subsequent therapy for patients having acquired resistance other than T790M mutation, and existence of consistent TOT with afatinib followed by osimertinib for Japanese patients comparing to Asian patients. Although retrospective analyses of Japanese patients enrolled in LUX-Lung 3 study (LL3) or other related studies showed consistent results between the studies, the available sample size was limited to be conclusive for the consistency. Therefore, the better sequence of treatment in use of EGFR tyrosine kinase inhibitor (TKI) is still unclear for patients with harboring EGFR mutation. Thus, this non-interventional study (NIS) observed TOT related to afatinib treatment in the first-line setting with TOT of subsequent therapies in patients with EGFR mutation- positive NSCLC.		
Research question and objectives:	The primary objective of this study was to confirm TOT related to afatinib treatment as first-line therapy (TOT1) in patients with EGFR mutation- positive NSCLC.		
Study design:	This was a non-interventional, multi-center study from existing data of patients treated with afatinib as the first-line treatment. The study involved secondary use of data which was extracted retrospectively once patients were enrolled into this study.		

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Setting:	This NIS study enrolled 857 patients at 40 sites in Japan. Patients information was chosen for patients treated with afatinib in the first-line setting in each study site after its launch on 7 May 2014 on a regular basis. In first round of data extraction, the data was extracted retrospectively once patients were enrolled into this study. A second round of data extraction was performed for additional follow-up one year after completion of first round data extraction. The data extraction was started on 01 Apr 2021 and ended on 07 Nov 2022.		
Subjects and study size, including dropouts:	Study enrolled 857 patients across 40 sites. Signed informed Consent Forms were obtained prior to a participation in the study. For eligible patients, the data extraction was started on 01 Apr 2021 and ended on 07 Nov 2022. Patients with EGFR mutation-positive advanced NSCLC, treated with afatinib in the first-line setting and >20 years of age at time of consent were included in this study. Patients were excluded if any had contraindication or previously treated in interventional trial with afatinib or having active brain metastases at start of afatinib treatment.		

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Variables and data sources:	The following data was extracted retrospectively. Patient and disease characteristics: - The status of informed consent and its date - Patient birthday - Gender - Smoking status, body weight and height, Eastern Cooperative Oncology Group (ECOG) performance status (PS) (if available), Stage (IIIb, IIIc or IV) at the start of afatinib treatment - Previous treatment status - Type of EGFR mutations at initial diagnosis of NSCLC Treatment pathways (details of treatments received): - Dates of start and end of afatinib treatment - Starting dose, modified dose of afatinib and dates of start and end for each modification - The progression status of brain metastasis in several lines - Type of EGFR mutations at the start of subsequent treatment in the second-line setting - Drug name of the subsequent treatment in the second-line setting - Dates of start and end of subsequent treatment in the second-line setting - Modified dose of subsequent treatment in the second-line setting and dates of start and end for each modification - Date of death - Reason for discontinuation of treatment in several lines - Last date of confirmed survival or death at second round data extraction Data was extracted from patients' existing data and recorded in electronic case report forms (eCRFs).		
Results:	The enrolled analysis set included a total of 857 patients, among these 805 (93.9%) were considered for the final analysis set. In overall analysis set, 659 (81.9%) patients were <75 years old and 586 (72.8%) had PS 0,1 at start of first-line treatment. The mean (standard deviation [SD]) period from diagnosis of NSCLC to initial dose of afatinib was 6.9 (18.1) months. At NSCLC diagnosis, Del19 type of EGFR was		

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reported in (n = 442, 54.9%) patients and majority of patients (n = 663, 82.4%) had common type of EGFR mutations than uncommon type. Patients who had uncommon mutation type status, 130 (91.5%) were belonged to Group 1 major. Metastasis at start of first-line treatment was known for (n = 770, 95.7%) patients among these 183 (22.7%) patients had reported brain metastasis. Almost all patients (n = 804, 99.9%) were not treated with any Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) agent before the first-line treatment.

The mean (SD) for the initial dose of afatinib was 36.6 (6.3) mg/day, 594 (73.8%) were started on afatinib 40 mg/day dose. Among patients who had received afatinib at initial dose of 10 mg, 20 mg, 30 mg and 40 mg/day; a higher number of patients (n = 477, 80.3%) who received afatinib at initial dose of 40 mg/day require modification in dose.

Among overall analysis set patients, re-evaluation of EGFR mutation at start of second-line treatment was performed in 385 (47.8%) patients; 139 (17.3%) patients had Del19 type of EGFR mutations; 205 (25.5%) had common mutation type and a majority of the patients (n = 131, 72.8%) belonged from Group 2 mutations at start of second-line treatment. Chemotherapy was the most common type of second-line treatment received by 307 (38.1%) patients followed by EGFR-TKI received by 261 (32.4%) patients. Among patients who received EGFR-TKI, osimertinib was received by (n = 167, 64.0%) patients followed by erlotinib (n = 51, 19.5%), gefitinib (n= 40, 15.3%), and only 3 (1.1%) patients received afatinib as second-line treatment.

Time from the start of afatinib as first-line treatment until the end of afatinib treatment (TOT1):

Among overall patients, the survival probability rate (95% confidence interval [CI]) against time to first-line treatment failure at 18 months was 0.39 (0.35-0.42) which was reduced to 0.15 (0.12-0.17) at 36 months. These survival probability rate were higher for subgroups of patients; <75 years age group, patients who had common EGFR mutation, Del19 EGFR mutation, Group 1 mutation subtype status at start of NSCLC diagnosis, also in patients who had ECOG PS (0/1) and no brain metastasis at start of first-line treatment.

	Time on treatment at start of first-line treatment (TOT): Among overall patients, the survival probability rate (95% CI) against time to treatment failure at 18 months was 0.58 (0.54-0.61) which was reduced to 0.30 (0.27-0.34) at 36 months. These survival probability rate against time to treatment failure at 18 months and 36 months were higher for subgroups of patients; <75 years age group, patients who had common EGFR mutation, Del19 EGFR mutation, Group 2 mutation subtype status at start of NSCLC diagnosis. Also with patients who had ECOG PS (0/1) and had no brain metastasis at start of first-line treatment. **Time on treatment at start of second-line treatment (TOT2):** Among overall patients, the survival probability rate (95% CI) against time to second-line treatment failure at 18 months was 0.17 (0.14-0.20) which was reduced to 0.09 (0.07-0.12) at 36 months. For subgroups, these survival probability rate were higher with patients who had uncommon type of EGFR mutation, other mutation subtype, and Group 2 mutation subtype status at the start of second-line treatment also, were higher with patients who had received EGFR-TKI treatment (osimertinib) and chemotherapy (in combination with platinum) at start of second-line treatment. **Overall survival (OS):** Among overall analysis set patients who had received afatinib at initial dose; the survival probability rate (95% CI) at 18 months was 0.80 (0.78-0.83) which was reduced to 0.54 (0.51-0.58) at 36 months. Among subgroups, these survival probability rate were higher for patients who had common type of EGFR mutation, Del19 mutation subtype, and Group 2 mutation subtype status at NSCLC diagnosis. Furthermore with patients who had ECOG PS (0/1) and no brain metastasis at start of first-line treatment. **The time to initial dose reduction of afatinib** For patients who had received afatinib at initial dose of 40 mg; among these patients survival probability rate (95% CI) against time to initial dose reduction of afatinib at 18 months and 36 months were 0.22 (0.19-0.26) and 0.20 (0.16- 0.24), respectively. These survival probability rate were higher for subgroups of patients who had uncommon type of EGFR mutation, other mutation subtype and Group 1 mutation subtype status at NSCLC diagnosis, and with patients who had ECOG PS (≥2) and brain metastasis at start of first-line treatment.
Discussion:	This observational study was undertaken in a broad range of Japanese patients with EGFR mutation-positive NSCLC treated in a real-world clinical practice setting. The results provide further evidence that afatinib is an effective 1L treatment option in Japan. Median TOT1 with afatinib was 13.4 months overall and 14.6 months in patients who initially received the approved dose of 40 mg/day. These findings are consistent with previous clinical trial data. In the Japanese sub-analysis of LUX-Lung 3, median time on treatment was 13.8 months (95% CI: 11.0–19.1).

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Names and affiliations of principal investigators:	[redacted]		