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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: GIOTRIF®			
Name of active ingredient: ACT code: L01XE13 Active substance: afatinib			
Report date: 04 Dec 2019	**Study number:** 1200.205	**Version/Revision:** V 1.0	**Version/Revision date:** N/A
Title of study:	**GIDEON:** ***GIOTRIF*®** ***in der Erstlinientherapie des fortgeschrittenen NSCLC mit aktivierenden EGFR-Mutationen*** GIOTRIF in First Line Therapy of Advanced NSCLC With EGFR-mutations Authors: Dr. [redacted], Dr. [redacted], Dr. [redacted], Germany Dr. [redacted], Germany		
Keywords:	Non-small cell lung cancer (NSCLC), Epidermal growth factor receptor (EGFR), Afatinib,		
Rationale and background:	Afatinib was approved in Europe as monotherapy for epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations. However, clinical trials do not provide a real-life picture on medication's efficacy and safety. In particular, older patients (>65 years) and patients with an Eastern Cooperative Oncology Group (ECOG) Performance Score of 2, which account for a majority of patients in clinical practice, are often not included or under-represented in clinical trials. This non-interventional study (NIS) was aimed to extend the knowledge on outcomes of first-line afatinib therapy in the clinical practice in Germany by prospectively investigating patient data routinely collected in medical practice. Real-world evidence was gathered to profile the impact of afatinib therapy employed in palliative care setting on disease progression, survival, safety, quality of life and symptom control in general NSCLC patient population.		

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Research question and objectives:	The primary objective of this NIS was to investigate the progression-free survival (PFS) rate at 12 months among the NSCLC patients treated with afatinib under routine clinical conditions. The secondary objectives were to evaluate tumor response rates, PFS (including time to progression on subsequent therapy), safety, toxicity and side effect profile, therapy duration, treatment modifications and symptom control. Additional objectives were to assess patient survival, management of specific side effects and documentation of quality of life (QoL) and tumor-related symptoms.		
Study design:	This was an open-label observational study according to §4, section 23 and §67, section 6 German Medicines Act. Patients were treated with afatinib in accordance with the terms of the marketing authorization for the first-line treatment in locally advanced or metastatic NSCLC driven by EGFR mutations.		
Setting:	The study was conducted by Boehringer Ingelheim Pharma GmbH & Co. KG in a routine care setting in 41 sites in Germany. The first coordinating investigator Prof. Dr. med. [redacted] who was replaced from April 2014 on by Prof. Dr. med. [redacted]). The study was submitted to the ethics committee of the Technical University of Dresden on 2nd of October 2013 and was accepted on 7th of October 2013. It was planned to enroll 150 patients treated at 50 oncological centers in Germany in the period between April 2014 and December 2016. Due to recruitment difficulties, the enrollment period had been increased for one year. Enrolled patients were to be observed for a period of three years and followed for 2 years.		
Subjects and study size, including dropouts:	The study included EGFR-TKI-naïve adult patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations who received afatinib as a first-line therapy according to the Summary of Product characteristics (SmPC). Inclusion criteria (IC) were: • EGFR- tyrosine kinase inhibitor (TKI)-naïve patients with histologically confirmed, locally advanced or metastatic NSCLC with activating EGFR-mutations		

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	• Age ≥ 18 years • No diagnostic or therapeutic measures beyond routine clinical practice were required • Patients for whom the treating physician decided to initiate treatment with afatinib • Written informed consent prior inclusion <u>Exclusion criteria (EC) were</u>: • Contraindication for afatinib according to the SmPC • Participation in another clinical study until 30 days after end of treatment • Prior systemic chemotherapy (neo-/adjuvant therapy was permitted) • Previous treatment with an EGFR-TKI • Patients not willing or not able to fill in quality of life questionnaires • Patients with missing or impaired legal capacity • Pregnancy Between 24th of March 2014 and 30th of December 2016, 161 patients at 41 sites were enrolled into the study. 152 patients received at least one dose of afatinib and were included in treated set (TS). Out of this number, six patients (3.9%) violated IC/EC criteria and therefore, 146 patients were included in per protocol set (PPS). Median age at registration of patients in TS was 67 years, the majority of patients were female (69.7%). Data on ethnicity and race were not collected.		
Variables and data sources:	Patient data were recorded on internet-based electronic case report forms: Baseline documentation included general patient characteristics, vital signs, laboratory parameters and blood count, date of diagnosis, primary tumor and metastasis location, risk factors, disease history, comorbidities and concomitant medication, ECOG performance score, histology, tumor, node and metastasis (TNM) status, EGFR mutation analysis, Charlson comorbidity index, details on surgery and pretreatments, and documentation of QoL and symptom control. Documentation of therapy included details on application of afatinib, ECOG performance status, vital signs, laboratory parameters and blood count, adverse events (AE) and serious AE (SAE), management of side effects, QoL and symptom control, tumor response and patient status at the end of afatinib treatment.		

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	Follow-up documentation included patient status and details on subsequent therapies.		
Results:	Primary outcome: 12-months PFS was achieved by 50.2% of patients in the PPS. Secondary outcomes: Objective response rate (ORR) was 74.6% and disease control rate (DCR) was 91.5% among the patients with available information on tumor response in the PPS. Median PFS amounted to 12.2 months (95% confidence interval (CI) 10.5-16 months). After progression on afatinib, at the time osimertinib was available and reimbursed in Germany, 28 out of 47 patients received osimertinib. Median duration of afatinib therapy amounted to 10.7 months (95% CI 0.4-48 months) and median time on treatment was 10.2 months (95% CI 0.4-48 months, for TS). 74.3%, 21.7% and 4% of patients received 40 mg, 30 mg or 20 mg starting dose of afatinib and 41.5%, 32.9% and 25.7% of patients received 30 mg, 40 mg or 20 mg final dose of the study drug. Dose of afatinib was modified in 61.8% of patients in the TS: 59.9% of patients had at least one dose reduction and 17.1% of patients had at least one dose increase. Analysis of symptom control by EORTC QLQ-C30/LC13 questionnaires revealed that median time to worsening (≥10 points increase from the baseline) was 33.9 months for cough (95% CI 17.9 - not reached), 22.2 months for dyspnea (95% CI 13.7 - not reached) and 18.3 months for pain (95% CI 9.2 - 23.7 months) in the TS. Further endpoints: Median OS for the PPS was 30.4 months (95% CI 23.6-39 months) and survival rates were 79.1% at 12 months and 57.7% at 24 months. Regarding the tumor-related symptoms, cough improved (≥10 points decrease from the baseline) or remained stable for 85.7% of patients from TS, dyspnea improved for 54.3%, short of breath remained stable for 65.7%, pain improved or remained stable for 62.9%, pain in chest and pain in arm/shoulder remained stable for 57.1% and 37.1%, respectively, and pain in other parts improved or remained stable for 54.3%. QoL/global health status improved (≥10 points decrease from the baseline) in 45.7% of patients in TS. Safety analysis: 98.7% of patients in the TS experienced treatment-emergent AE (TEAE),		

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defined as AE that occurred between start of treatment and 30 days after permanent discontinuation of therapy or end of study. 42.8% of patients had serious TEAE with the most frequent reasons for seriousness being hospitalization (39.5%), fatal outcome (5.3%) and life threatening status (4%). For 96.1% of patients, investigators judged that TEAE was related to the study drug. 19.7% of patients had serious drug-related TEAE. 23.7% and 11.8% of patients had TEAE or serious TEAE, respectively, leading to the discontinuation of afatinib. Most of adverse drug reactions (ADR) were of grade 2 (42.1% of patients) or grade 3 (35.5%). Diarrhea was the most commonly experienced ADR (82.9% of patients) followed by acneiformous dermatitis (37.5%), paronychia (25.7%), stomatitis (18,4%) and maculo-papular rash (17.8%). Most of serious ADR were of grade 3 (15.1%) or grade 2 (2%). Diarrhea was the most commonly experienced serious ADR (13.2%) followed by nausea (2.6%), vomiting, dehydration and acute kidney injury (2%, each).

Among afatinib ADRs, most of the patients experienced diarrhea (82.9%), stomatitis (18.4%) and paronychia (25.7%) while acneiformous dermatitis was the most frequent skin reaction (37.5%). Against diarrhea, measures taken most frequently were anti-diarrheal agents (72.4%) and intravenous supply of electrolytes and liquids (17.1%). However, in 26.3% of cases, no action against diarrhea was taken.
Prophylaxis against skin reactions was most often moisturing skin ointments (37.5%) or rehydrating skin care (21.1%), topical treatment most often included moisturing skin ointments (23%), other (22.4%) and ointments containing steroids (20.4%). Doxycycline was the most frequently applied systemic treatment (19.1%). Dermatologist treatment was received at least once by 25.6% of patients. Regarding skin reactions, 52% of patients received no prophylaxis, 57.2% did not receive topical treatment and 73% did not receive systemic treatment.

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Discussion:	Real-world data collected in this study confirmed that afatinib provides clinically relevant benefits and improves patient-reported outcomes. Obtained PFS and tumor response rates were comparable with clinical development data while OS was longer than that observed in clinical trials. Importantly, clinical outcomes among the patients with data on tumor response were generally in line with those reported by other observational studies. Symptom control was much better than previously demonstrated with a tendency towards longer time to worsening of dyspnea and pain. Furthermore, the percentage of patients that experienced AEs and ADRs in this study was comparable to what was observed in the pivotal clinical trials and other non-interventional studies investigating afatinib. Most of ADRs were predominantly gastrointestinal or dermatological in nature. The frequency of diarrhea and stomatitis was in line with previously available data, however, in comparison to previous studies, paronychia occurred less frequently in this study. In conclusion, obtained data confirmed a favorable benefit/risk ratio of afatinib therapy employed in everyday clinical practice in Germany. Advantages of afatinib extended to patient-reported outcomes since approximately half of patients saw improvements in QoL/global health status and tumor-related symptoms. Moreover, despite of dose de-escalation in almost two-thirds of patients, no noticeable negative impact on afatinib efficacy was observed. The ADRs observed in this study was in line with the known safety profile of afatinib, with diarrhea, acneiformous dermatitis being the most frequent. ADRs to afatinib were manageable by applying the pre-defined dose modification scheme. No new safety concerns were identified for afatinib. Finally, gathered results confirmed a considerable clinical potential of the use of third-generation EGFR-TKI in patients who acquired T790M mutation on first-line afatinib.		
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Names and affiliations of principal investigators:	Investigators of each participating site are listed in a stand-alone document (see Annex 1: List of stand-alone documents, which is available upon request).		