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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Giotrif®			
Name of active ingredient: afatinib (ATC code: L01EB03), gefitinib (L01XE02), erlotinib (L01XE03), osimertinib (L01XE35), antineoplastic agents, tyrosine kinase inhibitors			
Report date: 12th July 2021	**Study number:** 1200-0316	**Version/Revision:** Version 1.0	**Version/Revision date:** N/A
Title of study:	UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®		
Keywords:	Non-small-cell lung cancer; EGFRM+; Tyrosine kinase inhibitor; Real-world study		
Rationale and background:	Patients with non-small-cell lung cancer (NSCLC) represent a heterogeneous population; however, increased understanding of the molecular pathogenesis of the disease has allowed for new treatments using molecularly targeted anti-cancer agents. Currently, the most established target is the epidermal growth factor receptor (EGFR). Four EGFR tyrosine kinase inhibitors (TKIs; erlotinib, gefitinib, afatinib, and osimertinib) are currently globally available for the management of NSCLC. The two most frequent EGFR mutations (in-frame deletion in Exon 19 (Del19) and Point mutation in Exon 21 (L858R) account for >85% of all mutation-positive NSCLC cases and are known to confer sensitivity to EGFR TKIs, whereas the efficacy on uncommon mutation is still debated. Although several EGFR TKIs are available for the treatment of EGFR mutation-positive NSCLC, the development of acquired resistance is inevitable. Therefore, it is beneficial to consider the optimal sequence of EGFR TKIs to maximize their clinical benefit. There are limited real-world data with regard to EGFR mutated, advanced NSCLC who are EGFR TKI naïve; therefore, the aim of this study was to collect more information on the benefit of individual EGFR-TKIs treatment for the uncommon mutations and the overall benefit for the sequential EGFR TKI treatment with afatinib and osimertinib for the common EGFR mutations. These findings allow for evidence-based therapy decisions. Uncommon mutation cohort: There is convincing data for afatinib in many uncommon mutations (L861Q, G719X, and S768I), which resulted in regulatory approval by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). However, uncommon mutations are very heterogeneous, and more information on the benefit of individual EGFR-		

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	TKIs is needed to allow for evidence-based therapy decisions. Furthermore, little is known about the benefit of subsequent therapies and overall survival (OS). Sequencing cohort: It is still unclear which therapy sequence is the most beneficial for patients with EGFR mutated NSCLC. A recent global real-world study (GioTag) provided some insights into the outcomes of patients treated with the sequence afatinib followed by osimertinib. This study enrolled mainly Caucasian patients; study timelines and availability of drugs led to limited enrolment of long-term responders, and maturity of time to treatment failure was 52% and 31% for OS. Thus, more data from Asian patients and the longer availability of both drugs will provide more robust data with increased maturity. Various methodologies with different sensitivities can be used for mutational testing. The percentage of patients qualifying for the sequence afatinib followed by osimertinib patients depends on the methodology used. Moreover, little is known about the sensitivity of the different techniques for uncommon or compound mutation. Thus, it is of interest to learn more about the methods that have been used to identify uncommon mutations (including T790M). Data from the real-world setting would inform on the beneficial treatments in patients diagnosed with advanced NSCLC harbouring uncommon EGFR mutations and on the treatment sequence in patients diagnosed with advanced common EGFR mutation NSCLC.
Research question and objectives:	**Primary objective:** For both cohorts, the study aims to describe the time on treatment until its end or death. More specifically, this was evaluated for each cohort as follows: Uncommon mutation cohort: To determine the time on treatment of EGFR-TKIs as first or second-line therapy in NSCLC with uncommon Epidermal Growth Factor Receptor (EGFR) mutations. Time on treatment was defined from the start of EGFR-TKI until the end of EGFR-TKI treatment or death date by any cause. Sequencing cohort: To determine the time on treatment of afatinib (Giotrif®) as first-line therapy in patients with EGFR mutation-positive NSCLC followed by osimertinib in case the T790M resistance mutation was developed. Time on treatment was defined from the start of the first-line treatment until the end of the second-line treatment or death date by any cause. **Secondary objectives:** To determine the overall response rate, and overall survival. To describe methodology and the material (liquid vs. tissue) used for detection of uncommon/T790M mutation. To determine time on treatment until failure of second-line (uncommon mutation cohort only).
Study design:	Non-interventional, multi-country, multi-centre study based on existing data from medical records or electronic health records.
Setting:	A total of 56 study centers in 9 countries (Austria, France, Germany, Italy, Spain, United Kingdom, Japan, Korea Republic, and Taiwan Republic of China) were initiated in this non-interventional study. However, not all

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	sites enrolled patients. Conclusively, during the period comprised between December 2019 and November 2020: for Uncommon Mutation Cohort, 36 study centers in 9 countries participated, and enrolled 255 patients (246 were eligible); for Sequencing Cohort, 44 study centers in 9 countries participated, and enrolled 207 patients (191 were eligible). Chart abstraction date represents the end of observation for patients who were still alive at study inclusion; chart abstraction was performed in different days for different patients, therefore the chart abstraction date was different for each alive subject. Moreover, due to local IRB/EC restrictions in certain sites in Austria, South Korea, and Taiwan, data collection was not allowed after specific dates. For deceased patients at the time of study start, end of observation day was date of death; for untraceable patients at study start, end of observation day was the last date when the patient was known to be alive. Patients belonging to the Uncommon Mutation Cohort started the first-line treatment between 2007 and 2019, and data cut-off was on 16th July 2020 (greatest end of observation date for eligible patients of the Uncommon Mutation Cohort). For Sequencing Cohort, patients started first-line afatinib between 2014 and 2018, and data cut-off was on 23rd October 2020 (greatest end of observation date for eligible patients of the Sequencing Cohort).
Subjects and study size, including dropouts:	Sites with access to paper/electronic medical charts/electronic health records (EHR) were required to enroll patients who met all the following **inclusion criteria** (valid for both cohorts): 1. Adult patients 2. Diagnosed with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) naïve advanced EGFR mutated non-small cell lung cancer (NSCLC) 3. Treated for Epidermal Growth Factor Receptor (EGFR) mutated NSCLC within regular clinical practice 4. Informed and privacy consent signature obtained depending on local regulations More specific inclusion criteria for each cohort are the following: <u>Uncommon mutation cohort:</u> 5. Patients harbouring uncommon or compound EGFR mutations 6. Patients who started with either afatinib (Giotrif®), gefitinib (Iressa®), erlotinib (Tarceva®), or osimertinib (Tagrisso®) in the first- or second-line setting within regular clinical practice 7. Patients must have started EGFR-TKI treatment at least 12 months prior to data entry. <u>Sequencing cohort:</u> 5. Patients with common EGFR mutations (Del19, L858R) 6. Patients were treated with afatinib (Giotrif®) in the first-line setting and for acquired T790M mutation with osimertinib in the second line; 7. Patients must have started osimertinib treatment at least 10 months prior to data entry. Patients treated with osimertinib within an EAP/CUP were allowed.

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	Main exclusion criteria: 1. Patients treated for EGFR mutated NSCLC within a clinical trial or participated in the GioTag study. 2. Patients with active brain metastases at the start of EGFR-TKI therapy. 3. For uncommon mutation cohort: Patients treated with osimertinib with no further uncommon mutation than acquired T790M. **Uncommon Mutations Cohort:** A total of 255 patients were enrolled, of whom 246 (96.5%) were eligible. **Sequencing Cohort:** A total of 207 patients were enrolled, of whom 191 (92.3%) were eligible.
Variables and data sources:	Primary Outcome(s): Time on treatment (ToT) with EGFR-TKI(s) Secondary outcomes: Overall survival (OS), Overall Response Rate (ORR), methodology, and material used for mutational testing. Uncommon cohort only: time on treatment until failure of second-line (TTF2).
Results:	**Uncommon Mutations Cohort:** A total of 255 patients were enrolled in the Uncommon Mutation Cohort, of whom 246 (96.5%) were eligible. Among 9 ineligible patients, 3 were not harboring uncommon or compound EGFR mutations, 3 were treated for EGFR mutated NSCLC within a clinical trial, 2 had active brain metastases at start of EGFR-TKI therapy, and 1 had not started EGFR-TKI treatment at least 12 months prior to data entry. The median (Q1; Q3) duration of patients' observation (calculated as the difference between the end of observation date and the start date of first-line therapy) was 19.1 months (10.5; 31.3). Among 246 eligible patients, 41 (16.7%) patients were still on treatment with index EGFR-TKI at the end of observation. Out of 246 eligible patients, index EGFR-TKI was afatinib for 132 patients (53.7%), gefitinib for 70 (28.5%), erlotinib for 35 (14.2%), osimertinib for 7 (2.8%), and 2 additional patients received two sequential EGFR-TKIs within the index line (i.e., gefitinib followed by erlotinib, and afatinib followed by gefitinib). In particular, 226 patients (91.9%) had index EGFR-TKI as first-line treatment and 20 (8.1%) as second-line. During the observational period, 106 (43.1%) patients received only 1 line of NSCLC treatment, while patients receiving 2 treatment lines were 85 (34.6%), and patients receiving 3 or more lines were 55 (22.4%). The median (Q1; Q3) age at start of the first-line treatment was 69.5 years (60.0; 76.0) with more females (n=138; 56.1%) than males (n=108; 43.9%). The majority of patients were Asian (n=206; 90.0%). A total of 77 (33.3%) patients were previous smokers, and 25 (10.8%) were current smokers. The majority of patients (n=159, 83.7%) had an ECOG PS < 2 at start of the index line treatment.

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	The most frequent tumor histology at NSCLC diagnosis was adenocarcinoma (n= 239, 97.2%). At diagnosis or start of first-line treatment, 209 patients (85.0%) had NSCLC stage IV (others had stage IIIB-C). The median (Q1; Q3) duration of NSCLC until start of index EGFR-TKI therapy was 0.7 months (0.4; 1.7). At index EGFR-TKI therapy start, the most frequent locations of metastases were bones (n=83; 34.7%), lung contralateral (n=61; 25.5%), pleura (n=58; 24.3%) and lung ipsilateral (n=48; 20.1%). All patients treated with index EGFR-TKI in the first-line setting were tested for EGFR mutations; for 16 patients switching from first-line chemotherapy to second-line EGFR-TKI therapy (index line), EGFR mutational status was evaluated at the start of chemotherapy but was not re-evaluated at the start of EGFR-TKI treatment. Regarding EGFR mutational status at index therapy start or at first-line chemotherapy start (for the above-described 16 patients), 17 patients (6.9%) were T790M-positive, 29 (11.8%) had exon 20 insertion, 179 (72.8%) had major uncommon mutations (excluding those with T790M mutation and/or exon 20 insertions), 21 (8.5%) had other uncommon mutations; 82 patients (33.3%) had compound mutations (i.e., ≥ 2 EGFR mutations) in total. Among patients with EGFR mutational status tested at start of index line, solid biopsy was the most common approach for biological sampling (n=199; 87.7%), while the most frequent methodologies used for mutation testing were PCR-based techniques (n=146; 77.2%); a similar scenario was also observed in the 16 patients tested at first-line chemotherapy start. Considering best response to index line EGFR-TKI treatment, in 221 patients with available information, best response extent was CR in 3 patients (1.4%), PR in 93 (42.1%), SD or Non-CR/Non-PD in 90 (40.7%); 35 (15.8%) patients showed only disease progression. Overall response was achieved by 96 patients (43.4%). The median (Q1; Q3) duration of response was 10.0 months (4.8; 16.1) (n=56 patients with available information). Considering 223 patients with available information on best response to first-line treatment (any treatment received as first-line, not only EGFR-TKIs), CR was achieved in 3 (1.3%) patients, PR in 98 (43.9%) patients, SD or non-CR/Non-PD in 93 (41.7%) patients; 29 (13.0%) patients showed only disease progression. Overall response was achieved by 101 (45.3%) patients. The median (Q1; Q3) duration of response was 9.0 months (4.0; 14.0) (n=57 patients with available information). Among the 140 patients receiving more than one treatment line, considering 108 patients with available information on best response to second-line treatment (any treatment received as second-line, not only EGFR-TKIs), PR, SD or non-CR/Non-PD and disease progression only were achieved in 24 (22.2%), 53 (49.1%), and 31 (28.7%) patients, respectively. Overall response was achieved by 24 (22.2%) patients. The median (Q1; Q3) duration of response was 6.0 months (3.0; 14.5) (n=13 patients with available information).

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	The median time on treatment with index EGFR-TKI was 9.89 months (95% CI: 7.75-11.56), and 205 (83.3%) patients experienced treatment discontinuation/death during the observational period. Considering patients with more than one treatment line (n=140), median time to second-line treatment failure was 14.46 months (95% CI: 13.24-18.00), with 121 (86.4%) patients having second-line treatment discontinuation or death during the observational period. Median OS from start of the index EGFR-TKI therapy was 24.44 months (95% CI: 20.24-28.16), with 156 (63.4%) deceased patients. **Sequencing Cohort:** A total of 207 patients were enrolled in the Sequencing Cohort, of whom 191 (92.3%) were eligible. Among 16 ineligible patients, 8 were not treated with afatinib in the first-line setting or for acquired T790M mutation with osimertinib in the second line, 4 did not start osimertinib treatment at least 10 months prior to data entry, 2 had active brain metastases at start of EGFR-TKI therapy, 1 did not have common EGFR mutations, and 1 was treated for EGFR-mutated NSCLC within a clinical trial or participated in GioTag study. The median (Q1; Q3) duration of patients' observation (calculated as the difference between the end of observation date and the start date of first-line therapy) was 30.0 months (22.4; 39.8). Among 191 eligible patients, 51 (26.7%) patients were still on treatment with osimertinib at the end of observation. The median (Q1; Q3) age at start of first-line treatment was 62.0 years (53.0; 71.0) with more females (n=106; 55.5%) than males (n=85; 44.5%) enrolled. The majority of patients were Asian (n=118; 67.0%). A total of 52 (28.1%) patients were previous smokers and 12 (6.5%) were current smokers. Patients with ECOG PS < 2 were 139 (88.0%) and 132 (86.3%) at start of first-line and second-line treatment, respectively. The most frequent tumor histology at NSCLC diagnosis was adenocarcinoma (n=186; 97.4%). At diagnosis or start of first-line treatment, 176 patients (92.1%) had NSCLC stage IV (others had stage IIIB-C). The median (Q1; Q3) duration of NSCLC until start of first-line treatment was 0.6 months (0.3; 1.0). The median (Q1; Q3) duration of NSCLC until start of second-line treatment therapy was 16.8 months (12.3; 23.5). At first-line treatment start, the most frequent locations of metastases were bones (n=91; 48.1%), pleura (n=66; 34.9%) and lung contralateral (n=50; 26.5%) or ipsilateral (n=40, 21.2%). Regarding second-line treatment start, the most frequent locations of metastases were again bones (n=70; 36.6%), pleura (n=47; 24.6%) and lung contralateral (n=45; 23.6%) or ipsilateral (n=33, 17.3%). At start of first-line treatment, the most frequent EGFR common mutation was Del19 (n=135; 70.7%); all other patients had L858R (n=56; 29.3%); no patient had both mutations simultaneously. Solid biopsy was the most common approach for biological sampling (n=160; 86.5%), while the

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	most frequent methodologies used for mutation testing were PCR-based techniques (n=122; 81.3%). All patients developed acquired T790M mutation within second-line treatment start. Moreover, common mutations already detected at first-line treatment start were also maintained at second-line treatment start (except for one patient who no longer had Del19). Compared to the approaches for detection of EGFR mutations first-line start, solid biopsy was again the most common approach for biological sampling (n=93; 54.1%), but a higher proportion of patients was tested with liquid biopsy (n=57, 33.1%); methodologies used for mutation testing were in most cases PCR-based techniques (n=121; 86.4%). Patients receiving only 2 treatment lines during the observation period (i.e., afatinib followed by osimertinib) were 120 (62.8%), including 51 (26.7%) patients who were still on treatment with osimertinib at end of observation. Considering the 140 patients who stopped osimertinib treatment within end of observation, 71 (50.7%) patients received 3 to 9 total lines during the observational period. The median (Q1; Q3) duration of first-line afatinib treatment was 15.1 months (11.0; 21.0). Considering 178 patients with available information on best response to afatinib, CR was achieved in 3 (1.7%) patients, PR in 128 (71.9%), SD or non-CR/Non-PD in 47 (26.4%). Overall response was achieved by 131 (73.6%) patients. The median (Q1; Q3) duration of response was 9.0 months (3.0; 17.0) (n=71 patients with available information). Osimertinib was mainly used within regular clinical practice (n=187; 97.9%), whereas for 3 patients (1.6%) it was used through compassionate use program (CUP), and in 1 case (0.5%) details were not available. The median (Q1; Q3) duration of osimertinib treatment was 9.3 months (4.3, 15.3). Considering 166 patients with available information on best response to osimertinib, CR, PR, SD/non-CR/Non-PD and disease progression only were achieved in 2 (1.2%), 73 (44.0%), 69 (41.6%) and 22 (13.3%) patients, respectively. Overall response was achieved by 75 (45.2%) patients. The median time on treatment (i.e., time from afatinib start to osimertinib discontinuation/death) was 27.70 months (95% CI: 23.95, 30.23), and 140 patients (73.3%) experienced osimertinib discontinuation/death. Median OS calculated from afatinib start was 36.50 months (95% CI: 32.85, 41.76), with 102 deceased patients (53.4%). <u>Safety</u> Over 462 enrolled subjects, a total of 81 (17.5%) patients reported Adverse Drug Reactions (ADRs); a total of 81 (17.5%) patients reported ADRs to Giotrif®; 18 (3.9%) patients reported serious ADRs (none resulted in death).

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	In total, 330 ADRs occurred in 81 patients. Over the 330 ADRs that were reported, 322 (97.6%) were ADRs to Giotrif®, including 21 (6.4%) serious ADRs to Giotrif® (none resulted in death). The most-frequently reported ADRs included: gastrointestinal disorders (67 patients; 14.5%), of which diarrhoea (61 patients; 13.2%) and stomatitis (26 patients; 5.6%) were the most common ones; skin and subcutaneous tissue disorders (56 patients; 12.1%), among which rash (26 patients; 5.6%) and dermatitis acneiform (19 patients; 4.1%) were the most frequent ones; infections and infestations (33 patients; 7.1%), of whom paronychia (30 patients; 6.5%) was the most frequent one. Among the 322 reported total ADRs to Giotrif®, the most frequently-reported ADRs included: gastrointestinal disorders (n=121; 37.6%), of which diarrhoea (n=72; 22.4%) and stomatitis (n=31; 9.6%) were the most frequent ones; skin and subcutaneous tissue disorders (n=86; 26.7%), among which rash (n=32; 9.9%) and dermatitis acneiform (n=22; 6.8%) were the most frequent ones; infections and infestations (n=51; 15.8%), of whom paronychia (n=38; 11.8%) was the most frequent one. The ADRs to Giotrif® reported in this study, and their severity were consistent with the known safety profile of afatinib (Giotrif®). There were no new safety observations or concerns identified in this study.
Discussion:	**<u>Uncommon mutation cohort</u>** Afatinib is the standard of care (SoC) for most patients with uncommon mutations. The study supports the use of afatinib against major uncommon and compound EGFR mutations with additional broad activity against other uncommon EGFR mutations and some exon 20 insertions. It provides insights into treatment and testing strategies and emphasizes the need for broad testing and a clear description of mutations given their heterogeneity. **<u>Sequencing cohort</u>** The main study findings were in line with the expectations and well aligned to those obtained from the GioTag study, which can now be enriched with the Upswing data (obtained from a cohort composed especially of Asian patients). Therefore, the Upswing study allowed to further investigate the overall benefit for the sequential EGFR TKI treatment with afatinib and osimertinib for the common EGFR mutations. The ADRs to Giotrif® reported in this study, and their severity were consistent with the known safety profile of afatinib (Giotrif®). There were no new safety observations or concerns identified in this study. These findings complement the body of evidence in the real world for a better evidence-based therapy decision in NSCLC advanced EGFR-mutated setting.
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany