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1. ABSTRACT

Name of company:		Boehringer Ingelheim	
Name of finished medicinal product:		Gilotrif	
Name of active ingredient:		Afatinib Antineoplastic agents, tyrosinekinase inhibitors ATC code: L01XE13	
Report date: 17 SEP 2021	**Study number:** 1200-0335	**Version/Revision:** 1200-0335	**Version/Revision date:** 12/20/2021
Title of study:	Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring *NRG1* Gene Fusions		
Keywords:	Real-world, afatinib, NRG1		
Rationale and background:	The first neuregulin 1 (*NRG1)* fusion was reported by Fernandez-Cuesta et al in 2014 when they identified five *CD74-NRG1* fusions in invasive mucinous adenocarcinoma (IMA). Multiple tumor types with *NRG1* fusions have been described, including other lung, renal, head and neck, pancreatic, breast, ovarian, uterine, and prostate. The *CD74-NRG1* fusion provides an extracellular anchor for the epidermal growth factor (*EGF*) domain of *NRG1* to bind to ErbB3 (human epidermal growth factor receptor 3 (HER3]), leading to HER3 heterodimerization and activation of downstream signaling pathways resulting in oncogenesis. As such, targeted treatment with inhibitors of this pathway represents a possible therapeutic strategy. Afatinib, a pan-ErbB inhibitor, has been evaluated in preclinical models and in several case reports in patients with tumors harboring *NRG1* fusions who have achieved durable benefit with afatinib. *NRG1* fusions are rare, with an estimated overall frequency of ~0.2% to 0.8% across solid tumors and have a reported prevalence of up to 31% in lung IMA, making prospective clinical trials challenging.		

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Research questionand objectives:	**Research Questions:** 1. What are the characteristics of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib, and what are the characteristics of those treated with another systemic therapy? **Study Objectives:** 1. To describe the demographic and clinical characteristics of patients with NRG1 gene fusion-positive solid tumors treated with afatinib and of patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy. 2. To calculate the objective response rate (ORR) and duration of response (DOR) among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy 3. To estimate progression-free survival PFS, time on treatment (TOT), and time to progression (TTP) among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusions treated with other systemic therapy 4. To estimate OS among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy 5. To describe the incidence and severity of adverse events (AEs) among patients with NRG1 gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy
Study design:	This retrospective cohort study was conducted via a multi-site medical chart review of patients with *NRG1* gene fusion-positive solid tumors. Two cohorts of patients were identified: the first includes any patient with *NRG1* gene fusion-positive solid tumors who has received afatinib in any line of therapy (afatinib cohort). The second includes any patient with *NRG1* gene fusion-positive solid tumors who received another type of systemic therapy that was not afatinib (non-afatinib cohort). All patients must have initiated treatment after 01/01/2017 and before 03/31/2020. To remove potential bias, patients who died prior to 3 months following treatment initiation were still eligible. Data was collected between 11/30/2020 and 1/20/2021. Demographics, clinical characteristics, safety, and clinical outcomes (ORR, DOR, DOCB, TOT, TTP, PFS, OS, and AEs were described for both patient cohorts.
Population	**Inclusion Criteria:** • Adults, 18 years of age or older, at the time of diagnosis with any solid tumor.

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	• Confirmed *NRG1* gene fusion in any solid tumor. • Initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with *NRG1* gene fusion on or after 01/01/2017 and before 03/31/2020. • Followed up for ≥3 months after initiation of afatinib or other systemic therapy (unless deceased prior to 3 months of follow-up). **Exclusion Criteria:** • Treatment with any tyrosine kinase inhibitor (TKI)/ErbB-directed therapy other than afatinib
Setting:	Providers from the Cardinal Health Oncology Provider Extended Network (OPEN) were recruited to identify patients and complete electronic case report forms (eCRFs) of patients meeting the study selection criteria. All patients were required to have a confirmed NRG1 gene fusion in any solid tumor, initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with *NRG1* gene fusion on or after 01/01/2017 through 03/31/2020, and followed up for ≥3 months after initiation of afatinib or other systemic therapy (unless deceased prior to 3 months of follow-up). Data collection began on 11 NOV 2020 and concluded on 11 JAN 2021.
Subjects and studysize, including dropouts:	72 afatinib patients and 38 non-afatinib patients were included for a total sample size of 110.
Variables	The primary exposure of interest was treatment with afatinib. Two unmatched cohorts of patients were created: the afatinib-treated cohort includes patients with an *NRG1* gene fusion who received afatinib in any line of therapy; the second cohort includes any patient with an *NRG1* gene fusion who had never received afatinib prior to the date of data collection. Demographic and clinical characteristics (e.g., sex, age, payer type, US region, race/ethnicity, tumor type/characteristics, comorbidities, ECOG PS, *NRG1* gene fusion testing (e.g., timing, lab/location, results/partner), tumor-specific testing of interest (e.g., EGFR) were described in each cohort of patients at initiation of index therapy (i.e., afatinib or for those not treated with non-afatinib, the treatment received after NRG1 testing). Clinical outcomes measured in this study included median ORR, DOR, DOCB, TOT, TTP, PFS, OS, reported with a 95%-confidence interval (CI), and AEs.

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Data sources	De-identified, patient-level data was obtained from providers in the Cardinal Health Oncology Provider Extended Network (OPEN) who completed an eCRF for eligible patients. CHSS research operations recruited providers from OPEN to participate. OPEN is a community of over 7,000 oncologists, hematologists and urologists from across the U.S., with varying levels of time in practice, from practices both within and outside of group purchasing organizations. A subset of this provider group (~800) participates in retrospective observational research studies. All provider participation in the study was voluntary. Providers abstracted clinical and treatment related data as available from the patient's electronic health record (EHR) from the time of diagnosis of their primary malignancy through the last date of follow-up with the patient or death. Providers completed an eCRF for all eligible patients and were instructed to begin data abstraction with the first eligible patients, subsequently selecting consecutive patients moving forward. Required data elements were specified in the study inclusion/exclusion criteria; non-required data elements may have been missing/unknown. Providers may have abstracted data into the eCRF for both patients they personally managed/treated or those managed/treated by other providers within their practice. Providers were compensated for their time completing data abstraction into the eCRF only after subsequent data verification, as necessary. No source documents were provided to CHSS for verification; however, CHSS required duplicate data entry for a sample of patients' initial data collection to verify data point accuracy.
Results:	A total of 110 patients, n=72 afatinib, and n=38 non-afatinib were included in the final analytic dataset. In terms of demographic characteristics, the majority of patients within the afatinib cohort were male (58.3%) and White (66.7%), with the highest representation from the Northeast (36.1%) and West (36.1%) and a median age of 62 years at initiation of index therapy. Within the non-afatinib cohort, the majority of patients were male (52.6%) and White (57.9%), with the highest percentages of patients were from the South (63.2%). Median age of all patients at diagnosis was 62 years (inter quartile range, IQR 11) and the median age at the time of start of afatinib (or other index therapy) was 62.5 (IQR 11). In regard to clinical characteristics among afatinib-treated patients, the majority (70.8%) received afatinib as the second line (2L) of therapy. Most had an Eastern Cooperative Oncology Group (ECOG) score of 2 or greater (69.4%), had a past history of smoking (52.8%), and were stage IV at initial diagnosis (90.3%). Approximately 40% of patients had hypertension, 22.2% had chronic pulmonary disease, and 20.8% did not have

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	any comorbidities. Among all non-afatinib-treated patients, the majority received their index systemic therapy (i.e., time at which patient and treatment characteristics were collected) as the first line (1L) of therapy (94.7%). Further, the majority of patients had an ECOG score of 0 or 1 or greater (68.4%), had a past history of smoking (57.9%), and were stage IV at initial diagnosis (89.5%). The most common comorbidities in non-afatinib-treated patients were hypertension (55.3%), cardiovascular disease (36.8%), diabetes with chronic complications (31.6%) and chronic pulmonary disease (31.6%). 26.3% of non-afatinib-treated patients did not have any comorbidities. Keeping in mind most afatinib-treated patients received afatinib in 2L, the charted ORR to afatinib in any line was 37.5% (n=27). The calculated best response based on imaging was 34.7% (n=25). The DOR was 5.58 months. Keeping in mind most non-afatinib-treated patients were index in 1L, the ORR to index therapy was 76.3% (n=29). The calculated best response based on imaging was 71.1% (n=27). The DOR was 13.38 months. Among all afatinib-treated patients, median PFS was 5.49 months, median TOT was 5.42 months, and TTP was 5.49 months. For all non-afatinib-treated patients, median PFS was 12.89 months, median TOT was 5.08 months, and median TTP was 12.89 months. Median OS was 7.16 months in afatinib patients and 22.55 months in non-afatinib patients. Median DOCB in all patients (n=72) was 5.85 months. For 2L afatinib patients with known gene fusion partner (n=43) median DOCB was 5.43 months. In terms of adverse events, among all afatinib-treated patients during index treatment, 9.7% (n=7) experienced an adverse drug reaction ADR with a median 1 ADR. The first ADR reported was diarrhea, which was moderate in 57.1% of cases and severe in 42.9% of cases. All (100%) cases were attributed to treatment. For those that experienced the ADR, 85.7% (n=6) had a dose hold, dose delay, or schedule change, 42.9% (n=3) had a dose reduction, 14.3% (n=1) had a discontinuation of treatment, and 14.3% (n=1) had an unscheduled office visit or treatment. Among all non-afatinib patients during index treatment line, 21.1% (n=8) experienced an ADR with a median 1 ADR. Reported ADRs included febrile neutropenia (n=2, 25%), nausea/vomiting (n=1, 12.5%), neuropathy (n=1, 12.5%), neutropenia (n=2, 25%), and thrombocytopenia (n=2, 25%). Febrile neutropenia resulted in dose hold, dose delay, or schedule change for 1 patient, death in 1 patient, and inpatient hospitalization in 1 patient. Nausea/vomiting resulted in an unscheduled office visit for 1 patient. Neuropathy resulted in dose hold, dose delay, or schedule change for 1 patient. Neutropenia for dose reduction, dose hold/dose delay/schedule

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	change, and inpatient hospitalization for 1 patient in each outcome. Thrombocytopenia resulted in dose hold/dose delay/schedule change for 2 patients.
	There was an imbalance in line of treatment across the cohorts, rendering the non-afatinib cohort of limited context for the afatinib cohort. The majority of afatinib patients were on 2L therapy (70.8%) and the non-afatinib patients were largely on 1L therapy (94.7%). The current study had lower rates of adverse drug events (ADRs) compared to the randomized controlled trial for afatinib, although low severity ADRs which were not charted may have been missed. Both the non-afatinib and afatinib cohorts appear to have directionally better outcomes compared to comparators in the literature, although no statistical tests were performed, and the current study examined tumor site groups with 20 or fewer patients. The real-world data gathered by this study including demographic and clinical characteristics, outcomes, and adverse events of both afatinib and non-afatinib patients may be useful for informing prospective clinical trials of NRG1 fusion-driven tumors treated with afatinib.
Discussion:	This non-comparative, retrospective observational study identified patients with NRG1 positive solid tumors who had been treated with afatinib or another systemic therapy. The study provided new information as to the demographics and clinical characteristics of patients who were treated with afatinib or another systemic therapy in routine clinical practice. Across both afatinib and non-afatinib patients, the majority were White and male. There was an imbalance in line of treatment across the cohorts. The majority of afatinib patients were on 2L therapy (70.8%) and the non-afatinib patients were largely on 1L therapy (94.7%). Without formal comparisons performed, it appears that overall, there were lower rates of ADRs in the current study compared to the randomized controlled trial for afatinib, although less severe ADRs may not have been charted and therefore not captured in this study. Both the non-afatinib and afatinib cohorts appear to have directionally better outcomes compared to comparable extant literature, although no statistical tests were performed, and the current study examined tumor site groups with 20 or fewer patients. Future research is warranted to generate evidence comparing afatinib and non-afatinib patient cohorts. Additional research is needed to examine if gene fusion status may possibly be prognostic. Prospective clinical trials with large numbers of NRG1 fusion-driven tumors of diverse origins treated with afatinib are also warranted.
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