TITLE PAGE

Protocol for non-interventional studies based on existing data

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BI Study Number:	CTMS 1200.335
BI Investigational Product(s):	Gilotrif® (afatinib)
Title:	Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring *NRG1* Gene Fusions
Protocol version identifier:	v1.0
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Active substance:	Afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13
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Product reference:	20 mg: NDC: 0597-0141-30 30 mg: NDC: 0597-0137-30 40 mg: NDC: 0597-0138-30
Procedure number:	
Joint PASS:	
Research question and 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 ORR and 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 PFS (and TOT, 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
Country(-ies) of study:	United States
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Marketing authorization holder(s):	[redacted]
MAH contact person:	
Date:	8-MAY-2020
Page 2 of 45	

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

1L	First-line (therapy)
AACR	American Association for Cancer Research
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim Pharmaceuticals
[redacted]	[redacted]
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Event
Del19	exon 19 deletion mutation
DOCB	Duration of clinical benefit
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGFR+	EGFR mutation-positive
EHR	Electronic Health Record
EMR	Electronic Medical Record
FAE	Fatal adverse event
FDA	United States Food & Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HER2	human epidermal growth factor receptor-2
HER3	human epidermal growth factor receptor-3
IMA	Invasive mucinous adenocarcinoma
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
L858R	exon 21 point mutation
MMR	Mismatch Repair Genes
MSI	Microsatellite Instable
NIS	Non-interventional study
NSCLC	Non-small cell lung cancer
NRG1	Neuregulin-1
[redacted]	[redacted]
ORR	Overall response rate
OS	Overall survival
PHI	Protected Health Information
PFS	Progression-free survival
PD	Progressive disease
PR	Partial response
PS	Performance Status

RECIST	Response Evaluation Criteria In Solid Tumors
RCT	Randomized controlled trial
RWE	Real-world evidence
SAE	Serious adverse event
SD	Stable disease
SE	Standard Error
SJS	Stevens Johnson Syndrome
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEN	Toxic Epidermal Necrolysis
TKI	Tyrosine kinase inhibitor
TOT	Time on treatment
TTF	Time to treatment failure
TTP	Time to progression
US	United States

3. RESPONSIBLE PARTIES

Principal/Co-Investigators	[redacted]
Clinical Investigators	[redacted] and Senior Medical [redacted] [redacted] [redacted] Team [redacted] Medicine [redacted] [redacted] Senior Global Medical Advisor [redacted]
Study Statistician	[redacted]
Project [redacted]	[redacted] Project [redacted]
Research [redacted]	[redacted] Consultant, [redacted]
Clinical Analyst	[redacted]

Regulatory Affairs	[redacted]

4. ABSTRACT

Name of company:			
Boehringer Ingelheim			
Name of finished medicinal product: Gilotrif®			
Name of active ingredient: afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13			
Protocol date: 17 March 2020	**Study number:** CTMS 1200.335	**Version/Revision:** 1.0	**Version/Revision date:** 17 March 2020
Title of study:	Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring *NRG1* Gene Fusions		
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 (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. Obtaining real-world data describing the real-world outcomes associated with afatinib in patients with *NRG1* fusion-positive solid tumors is valuable, and such data may be used in supplemental applications for label expansion requests to the U.S. FDA and other agencies.		

Research question and 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 ORR and 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 PFS (and TOT, 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 will be conducted via a multi-site medical chart review of patients with *NRG1* gene fusion-positive solid tumors. Two cohorts of patients will be 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 has not received afatinib in any line of therapy (other systemic therapy 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 are still eligible. Data collection is anticipated to occur in Q3/Q4 of 2020, allowing for a minimum follow-up of approximately 3 months. Demographics, clinical characteristics, safety, and clinical outcomes (ORR, DOR, DOCB, TOT, TTP, PFS, OS, and AEs will be described for both patient cohorts.

Population:	**Inclusion Criteria** • Adults, 18 years of age or older, at the time of diagnosis with any solid tumor. • 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 TKI/ErbB-directed therapy other than afatinib
Variables:	The primary exposure of interest is treatment with afatinib. Two unmatched cohorts of patients will be 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]) will be described in each cohort of patients. Clinical outcomes to be measured in this study include ORR, DOR, DOCB, TOT, TTP, PFS, OS, and AEs.

Data sources:	De-identified, patient-level data will be obtained from providers in the [redacted] who will complete an eCRF for eligible patients. [redacted] will recruit providers from [redacted] to participate. [redacted] 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 is voluntary. Providers will abstract clinical and treatment related data as available from the patient's EHR from the time of diagnosis of their primary malignancy through the last date of follow-up with the patient or death. Providers will complete an eCRF for all eligible patients and will begin data abstraction with the first eligible patients, subsequently selecting consecutive patients moving forward. Required data elements are specified in the study inclusion/exclusion criteria; non-required data elements may be missing/unknown. Providers may abstract data into the eCRF for both patients they personally managed/treated or those managed/treated by other providers within their practice. Providers are compensated for their time completing data abstraction into the eCRF only after subsequent data verification, as necessary. No source documents will be provided to [redacted] for verification; however, [redacted] will require duplicate data entry for a sample of patients' initial data collection to verify data point accuracy.

Study size:	The total target number of patients is up to120 patients, including up to 70 patients with an *NRG1* gene fusion-positive solid tumor treated with afatinib and up to 50 patients with an *NRG1* gene fusion-positive solid tumor who had not received afatinib at the time of data collection. The target number of patients was based on the results of a pilot feasibility study conducted by [redacted] with Boehringer Ingelheim (BI). In December 2019, [redacted] conducted outreach to approximately 800 providers in [redacted] to inquire as to the number of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib whom they had personally managed or who were cared for at their practice. Providers were presented with similar inclusion criteria as those described above. In total, 12 oncologists completed short eCRFs describing a total of 108 patients. Of those, 67 (62%) were treated with afatinib and 41 (38%) had not received afatinib. Based on the feasibility study, [redacted] will target up to 70 afatinib-treated patients with *NRG1* gene fusion-positive solid tumors and up to 50 patients with *NRG1* gene fusion-positive solid tumors who had not received afatinib. Although the feasibility study did not identify this number of patients, further recruitment of non-responders to the survey invitation will be used to achieve the target number of patients planned for this study. In lieu of a comparative analysis between the afatinib-treated and non-afatinib treated patients are exploratory, the precision of estimates involving 70 patients in the afatinib-treated cohort would be associated with a standard error of any bivariate response variable between 6.0% and 13.9%.

Data analysis:

Demographic and clinical characteristics will be reported via descriptive analyses, including counts and frequencies for dichotomous and categorical variables, while measures of centrality (mean, median) and spread (min, max, standard deviation, interquartile range, as appropriate) will be used for continuous variables. These characteristics will be described at the time of initial diagnosis of advance/metastatic disease and at the time of initiation of each line of therapy received.

For disease response, the point estimate for ORR and associated 95% confidence interval will be calculated for each cohort. The Kaplan-Meier method will be used to estimate any time to event outcome including DOR, DOCB, TOT, TTP, PFS, and OS to account for any right censoring (e.g., patient had not discontinued therapy, patient had not progressed or died).

Given the small number of patients targeted for study inclusion and anticipated differences in baseline characteristics between afatinib-treated and patients treated with other systemic therapies, statistical comparisons are not planned. In lieu of statistical comparisons between cohorts, the non-afatinib cohort will provide context for interpreting results among those treated with afatinib. Specifically, this context includes what patients with *NRG1* gene fusions not treated with afatinib look like, how they are managed and treated, and what their clinical outcomes look like. The non-afatinib cohort will provide a broader understanding of *NRG1* gene fusions among patients with solid tumors, for which limited evidence currently exists.

Incidence and severity of AEs will be summarized and displayed in number/percentage. All safety endpoints will be analysed descriptively.

Milestones:

Task	**Start Date**
Internal approval of study synopsis	March 2020
Internal approval of study protocol	May 2020
Submission of study protocol to FDA	May 2020
FDA feedback received	June 2020
Finalization of protocol	July 2020
IRB submission and review	July 2020
Recruitment & data collection	Q3/Q4 2020
Demographics & clinical characteristics	November 2020
Outcomes assessment	November 2020
Final report	December 2020

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	**Planned Completion Date**
Internal approval of study synopsis	March 2020
Internal approval of study protocol	May 2020
Submission of study protocol to FDA	May 2020
FDA feedback received	June 2020
Finalization of protocol	July 2020
IRB submission and review	July 2020
Recruitment & data collection	Q3/Q4 2020
Demographics & clinical characteristics	November 2020
Outcomes assessment	November 2020
Final report	December 2020

7. RATIONALE AND BACKGROUND

The epidermal growth factor receptor (*EGFR*) signaling pathway regulates apoptosis and proliferation in normal cells. An *EGFR* family component of the of tyrosine kinase ligands, neuregulin-1 (*NRG1*), induces the proliferation, differentiation, and survival of cells in epithelial, neuronal, and myocytic tissue types, among others. The first *NRG1* fusion was reported by Fernandez-Cuesta et al. in 2014 when they identified five *CD74-NRG1* fusions in invasive mucinous adenocarcinoma (IMA).[1] The *CD74-NRG1* fusion provides an extracellular anchor for the epidermal growth factor (EGF) domain of *NRG1* to bind to ErbB3 (HER3) leading to HER3 heterodimerization and activation of downstream signaling pathways leading to oncogenesis.[2] 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[3] and in several case reports in patients with tumors harboring a *NRG1* fusions that achieved durable benefit with afatinib.[4-6]

NRG1 fusions are rare, with an estimated overall frequency of ~0.2% across solid tumors[7] and have a reported prevalence of up to 31% in lung IMA[8] making prospective clinical trials challenging. In addition to IMA, other tumor types with *NRG1* gene fusions that have been described include cholangiocarcinoma (0.8% of cases tested), thyroid cancer (0.7%), ovarian cancer (0.5%), pancreatic cancer (0.4%), non-small cell lung cancer (NSCLC; 0.3%), breast cancer (0.2%), sarcomas (0.2%), and sinonasal teratocarcinoma,[9] as well as renal cell carcinoma, head and neck cancer, uterine cancer, and prostate cancer.[10] While the incidence of *NRG1* gene fusions is only around 0.2% of all solid tumors, this represents approximately 3,500 new cases per year.

Results presented at the American Association for Cancer Research (AACR) Annual Meeting 2019 showed tarloxotinib to be active against *NRG1* gene fusion cancers, irrespective of site of origin. It is believed that afatinib may have similar activity across sites of cancer associated with *NRG1* gene fusions. Recent case reports presented some of the first evidence that patients with *NRG1* gene fusions who were treated with afatinib had durable responses.[5] While the first reports emerged in lung cancer,[5] further research has implicated other solid tumors.[6] These findings indicate that malignancies associated with *NRG1* gene fusions may benefit from treatment with afatinib.

Afatinib (Gilotrif®) was initially approved in 2013 by the U.S. Food & Drug Administration (FDA) for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; this indication was broadened in 2018 to include non-resistant EGFR mutations. Additionally, afatinib was approved in 2016 for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy. Obtaining real-world data describing the real-world outcomes associated with afatinib use in patients with *NRG1* fusion-positive across a range of solid tumors may be used in supplemental applications for label expansion requests to the FDA and other agencies. This study aims to provide real-world evidence on the real-world clinical outcomes associated with afatinib use among patients with *NRG1* gene fusions across a range of solid tumors, as well as real-world data among patients with *NRG1* gene fusions treated with other systemic therapies.

8. RESEARCH QUESTIONS AND OBJECTIVES

Limited data on durable responses in patients with *NRG1* gene fusion-positive solid tumors have been reported with afatinib. Beyond these data, no comprehensive evaluation has been conducted of patients harboring *NRG1* gene fusions treated with afatinib or other systemic therapy, in any line of therapy, to describe patient characteristics and clinical outcomes associated with afatinib use. This study aims to answer these questions by achieving the objectives stated below. As this study is descriptive in nature, no *a priori* hypothesis will be tested.

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 ORR and 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 PFS (and TOT, 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 AEs among patients with *NRG1* gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, retrospective, US, multi-site, cohort study based on existing data from medical records of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib or other systemic therapy. Two cohorts of patients will be identified. The first includes any patient with *NRG1* gene fusion-positive solid tumors who has received afatinib in any line of therapy (afatinib cohort) between 01/01/2017 and 03/31/2020. The second includes any patient with *NRG1* gene fusion-positive solid tumors who has not received afatinib in any line of therapy (other systemic therapy cohort) during the same period and no history of afatinib use. Follow-up will include at least 3 months after initiation of afatinib or other systemic therapy, unless a patient died prior to 3 months of follow-up.

In total, up to 120 patients with *NRG1* gene fusion-positive solid tumors will be selected for this study, of whom up to 70 will be afatinib-treated and up to 50 will be treated with other systemic therapy. Study objectives are to describe these patients and calculate the ORR in each group, as well as to estimate PFS, TOT, TTP, OS, DOR, and DOCB along with describing the incidence and severity of AEs among patients in the two cohorts. Data to be collect through this medical chart review include patient demographics, clinical characteristics at the time of diagnosis/initiation of a line of therapy, treatment-related data points (dates of initiation, discontinuation, dosing), AEs occurring during therapy, disease response, date of progression and/or death.

Given the small number of patients targeted for study inclusion and anticipated differences in baseline characteristics between afatinib-treated and patients treated with other systemic therapies, statistical comparisons are not planned. In lieu of statistical comparisons between cohorts, the non-afatinib arm will provide context for interpreting results among those treated with afatinib. Specifically, this context includes what patients with *NRG1* gene fusions not treated with afatinib look like, how they are managed and treated, and what their clinical outcomes look like. The non-afatinib arm will provide a broader understanding of *NRG1* gene fusions among patients with solid tumors

Data collection is anticipated to begin in the third/fourth quarter of 2020, allowing for a minimum follow-up period of 3 months. All patients are required to have initiated index therapy (i.e., afatinib in any line; other systemic therapy among those without any history of afatinib) between 01/01/2017 and 03/31/2020. As such, the maximum follow-up period is approximately 39 months. The index date is the date of initiation of afatinib or other systemic therapy between 01/01/2017 and 03/31/2020 for the other systemic therapy cohort.

9.2 SETTING

Approximately 20 or more unique providers will participate in this research study. To minimize potential bias, the maximum number of patients each provider may select and complete data abstraction for is capped at 30; for any provider who submits >10 patients, their data will be reviewed in detail by a clinician and analyst to identify any data quality issues (see Section **9.8.2 Data Validation** for further details on data quality assurance and control measures). Data

will be collected through an electronic case report form (eCRF) completed by the patients' providers who volunteer to participate in the study. Providers will be compensated at fair market value for the time to complete data abstraction and quality control procedures, which are estimated to take up to 1 hour per patient.

Recruitment of providers will be conducted electronically. Providers who responded to an initial feasibility request and reported treating potentially eligible patients will be contacted and invited to participate. Recruitment to fill the up-to-120-patient quota will run for 4 weeks from the date of recruitment launch. During that time, the per-cohort quotas will be electronically monitored to ensure that the final number of patients achieves up to 70 patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and up to 50 with an *NRG1* gene fusion-positive solid tumor not treated with afatinib at the time of data collection. As recruitment for a cohort is completed, no further patient data entry will be allowed for that cohort; however, providers actively completing an eCRF at the time of quota close for a cohort will be allowed to complete that eCRF, and the total number of patients per cohort may exceed the quotas.

Providers will be asked to identify all eligible patients, and starting with the earliest index date, chronologically select consecutive patients meeting the eligibility criteria and complete the data abstraction. The eCRF is structured to allow data collection regarding patient clinical history at the time of initial diagnosis of their solid tumor, initiation of index therapy (including dates of dose starts, stops, and interruptions), response to therapy, dates of disease progression, AEs, (including dates of onset, recovery, and reported deaths).

9.2.1 Provider/Site/Patient Selection

Provider Eligibility

Providers who meet the following criteria will be eligible to participate:

1) Are board-certified oncologist/hematologist.
2) Have treated/are treating at least one eligible patient with an *NRG1* fusion-positive solid tumor.
3) Are able to participate in research approved by an external institutional review board (IRB).
4) Agree to participate in data quality assurance/control processes.

Providers will select patients meeting the study eligibility criteria as described below. Providers will be asked to select eligible patients chronologically, starting with the first patient who first initiated any line of afatinib or chemotherapy, on or after 01/01/2017 through 03/31/2020.

Patient Eligibility

Inclusion Criteria:

- Adults, 18 years of age or older, at the time of diagnosis with any solid tumor.
- 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.

- 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 TKI/ErbB-directed therapy other than afatinib

9.3 VARIABLES

9.3.1 Exposures

The primary exposure of interest is treatment with afatinib. Two cohorts of patients will be created: the afatinib-treated cohort includes patients with an *NRG1* gene fusion-positive solid tumor who had received afatinib in any line of therapy; the second cohort includes patients with an *NRG1* gene fusion-positive solid tumor who had not received afatinib prior to the date of data collection. Patients treated with afatinib monotherapy and their outcomes will be described in addition to the two main aforementioned treatment groups.

9.3.2 Outcomes

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 will be summarized for each cohort. These variables serve as outcomes in terms of fulfilling study objectives. These variables also serve as covariates to contextualize other study outcomes (e.g., ORR, DOR, DOCB, PFS, TOT, TTP, OS, AEs).

Table 1. Patient demographics and clinical characteristics.

Characteristic	Definition
Sex	Patient sex, as charted
Age(s)	Age at diagnosis of solid tumor and age at initiation of afatinib or other systemic therapy
Region	US census region of patient: Northeast, South, Midwest, West
Race/ethnicity	Race and ethnicity of patient, as charted
Tumor type	Description/classification of primary tumor of patient (e.g., NSCLC, cholangiocarcinoma, pancreatic cancer)
ECOG PS	ECOG PS of patient at initiation of afatinib or other systemic therapy
Comorbidities	Comorbidities present at initiation of afatinib or other systemic therapy, following Charlson comorbidity index
Stage	Stage of tumor at initiation of afatinib or other systemic therapy
NRG1 results	Date of *NRG1* gene fusion test; laboratory performing test (e.g., academic, reference, in-house lab; name of lab); *NRG1* gene fusion partner
Other biomarkers	Tumor-specific biomarkers tested and their results (e.g., MSI/MMR, EGFR, HER2)

The ORR 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 will be calculated as the proportion of patients with a complete response (CR) or partial response (PR) out of all patients (CR+PR/all patients) (see **Table 2** below). Disease response for determining the ORR will be reported as recorded in the patient's EHR, including the date of radiographic imaging used to substantiate the patient's initial and best response to therapy. Providers will indicate whether the patient experienced a CR, PR, stable disease (SD), or progressive disease (PD). No independent blinded review of radiology studies will be conducted. Lesion measurements at baseline (initiation of afatinib; initiation of other systemic therapy for non-afatinib treated patients), initial response, and best response will be abstracted as available. Changes in the number, locations, and sizes of lesions at initial and best response to therapy will be evaluated by [redacted] using RECIST v1.1 guidelines. The sum of lesion measurements will be assessed at baseline and at follow-up scans to calculate the percent change in sum of target lesions, as well as account for new lesions on follow-up scan in order to classify response by RECIST v1.1 criteria. Actual scan images will not be reviewed; the calculation of real-world disease response will be based on the lesion measurements provided. Other outcomes include PFS, TOT, TTP, OS, DOR, DOCB, AEs. Definitions of these outcomes are shown in **Table 2**.

Table 2. Study outcomes and definitions.

Outcome	Definition
ORR	Proportion of patients with a complete response (CR) or partial response (PR) out of all patients (CR+PR/all patients) at initial response assessment and best response
DOCB	Duration of clinical benefit (DOCB) will be calculated as the time from initial response (for any patient with a complete, partial, or stable disease response initially) until the earliest of either disease progression or death. Patients who discontinue therapy due to a reason other than progression will be censored on the date of discontinuation. Patients still on therapy at the time of data cut-off will be censored on their last visit date.
DOR	Duration of response will be calculated as the time from initial response (for any patient with a complete or partial response initially) until the earliest of either disease progression or death. Patients who discontinue therapy due to a reason other than progression will be censored on the date of discontinuation. Patients still on therapy at the time of data cut-off will be censored on their last visit date.
TOT	Time from initiation of a line of therapy until discontinuation for any reason; patients on therapy at the time of data cut-off will be censored on the last date of treatment.
TTP	Time from initiation of a line of therapy until discontinuation due to disease progression; patients on therapy or those who discontinued due to a reason other than disease progression will be censored on the last date of treatment.

PFS	Time from initiation of a line of therapy until disease progression or death; patients on therapy at the time of data cut-off will be censored on the last date of treatment. Patients who discontinue a line of therapy for a reason other than disease progression but who subsequently die prior to the receipt of any other therapy will be considered an event on the date of death.
OS	Time from initiation of any therapy in the metastatic setting until death; patients alive at the time of data cut-off will be censored on the last date the patient was seen by the provider/clinic.
AE	An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs from a prepopulated list (including "other, please specify") during each line of therapy will be indicated by providers. The number and proportion of patients experiencing each AE reported during afatinib or other systemic therapy will be reported. See Section 11.1 and Table 3 for further details.

In addition to TOT, to further characterize treatment patterns for those treated with afatinib and those treated with other systemic therapy, the following will be collected (and calculated based on the collected data):

- Treatment history (i.e., regimens, duration, number of cycles, sequence)
- Starting dose of afatinib or other systemic therapy
- Dose modifications of afatinib or other systemic therapy (i.e., dose reductions and their timing, dose increases and their timing, dose delays and their duration and timing)
- Rationale for afatinib or other systemic therapy discontinuation

AEs will be collected and analyzed in the Clinical Study Report. Providers will be shown information describing what constitutes an AE/ADR/SAE/FAE per BI policies. The processes for safety reporting and analysis of the safety data will be implemented and conducted as per the BI non-interventional study (NIS) standard operating procedures. [redacted] will complete any reporting of events to BI per event reporting protocols.

The diagnosis, time, attribution (treatment-related or not per provider interpretation) and severity of the reported AEs during index therapy will be collected. If death is cited as rationale for discontinuation then provider will abstract data related to date of death, cause of death.

Table 3. Adverse events data collection.

Variable	**Definition / response options**
AEs during a given line of therapy	During each line of therapy, providers will indicate the AE that occurred including severity.
Start date of AE	Date each AE occurred

Severity (see section 11.1)	Severity of each AE, as assessed by the provider, provided the following guidance: • Mild (mild symptoms; clinical or diagnostic observations only [e.g. lab work]; intervention not performed) • Moderate (minimal, local or noninvasive intervention performed [e.g., administration of fluids] • Severe (medically significant ranging from not immediately life-threatening, life-threatening consequences, to death related to AE; [e.g., extensive monitoring, hospitalization or prolongation of hospitalization])
Resolution	Outcome of each AE will be collected as: • Recovered/Resolved • Recovered/Resolved with sequelae • Not yet recovered/Not yet resolved • Fatal • Unknown
Outcome	For all AEs, the outcome of the AE, regardless of severity indicated, will be assessed by participating providers. These outcomes will allow for the classification of serious and fatal AEs as defined in Section 11 • Dose reduction • Dose hold/dose delay/schedule change • Discontinuation of treatment • Unscheduled office visit/treatment • Resulting in death • Life-threatening • Required inpatient hospitalization • Resulted in persistent or significant disability • Prolonged existing hospitalization
End date of AE	Date AE resolved/patient recovered (if resolved/recovered)
Causal relationship of AE to treatment	See section 11.2 for guidance on assessing causal relationship (i.e., afatinib or other systemic therapy)

9.3.3 Covariates

Patient demographics clinical characteristics will be described in each cohort of patients. As described above, these variables will be summarized descriptively as study outcomes and also

considered as covariates to contextualize the clinical outcomes of the study (e.g., ORR, DOR, PFS, TOT, OS, AEs). These variables are described in Section **9.3.2 Outcomes**, above.

9.4 DATA SOURCES

All study data will be entered by the investigators into the eCRF. The eCRF captures data for each of the study variables described in **Section 9.3 - Variables**. The eCRF is designed to allow providers to efficiently move through the patient chart or EMR based on the journey of the patient through the course of disease. The eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information (PHI).

De-identified, patient-level data will be obtained from providers in the [redacted] who will complete an electronic case report form (eCRF) for eligible patients. [redacted] will recruit providers from [redacted] to participate. [redacted] 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 group (~800) participates in retrospective observational research studies. All provider participation in the study is voluntary.

To be eligible to participate, providers must have treated at least one patient meeting the study eligibility criteria, be able to participate in research approved by an external institutional review board (IRB), and agree to participate in data quality control processes. No provider at practices that require local IRB approval at the practice will be eligible to participate. A waiver of obtaining patient consent will be sought for the study. No protected health information (PHI) beyond dates of diagnosis, treatments, and outcomes will be collected.

Providers will abstract demographic-, clinical-, and treatment- related data as available from the patient's electronic health record (EHR), starting from the time of primary malignancy diagnosis through the last date of follow-up with the patient or death. Providers will complete an eCRF for all eligible patients and will begin data abstraction beginning with the first eligible patients and select consecutive patients moving forward in time. Data elements that are required are specified in the study inclusion/exclusion criteria; non-required data elements may be missing/unknown. Providers may abstract data into the eCRF for both patients they personally managed/treated or those managed/treated by other providers within their practice.

9.4.1 Source Documents

Providers are compensated for their time completing data abstraction into the eCRF and subsequent data verification as necessary. No source documents will be provided to [redacted] for verification; however, [redacted] will require duplicate data entry for a sample of patients (see **Section 9.8.2 Data Validation**) after initial data collection to verify data point accuracy.

9.4.2 Dataset and Records

9.5 STUDY SIZE

The total target number of patients is up to 120 patients, including up to 70 patients with an *NRG1* gene fusion-positive solid tumor treated with afatinib and up to 50 patients with an *NRG1* gene fusion-positive solid tumor who had not received afatinib at the time of data collection. The target number of patients was based on the results of a pilot feasibility study conducted by [redacted] with BI.

In December 2019, [redacted] conducted outreach to approximately 800 providers in [redacted] to inquire as to the number of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib they had personally managed or who were cared for at their practice. Providers were presented with similar inclusion criteria as those described herein. In total, 12 oncologists completed short eCRFs describing a total of 108 patients. Of the 108, 67 patients were treated with afatinib and 41 had not received afatinib therapy.

Based on the feasibility study, [redacted] will target number of patients of up to 70 afatinib-treated patients with *NRG1* gene fusion-positive solid tumors and up to 50 patients with *NRG1* gene fusion-positive solid tumors who have not received afatinib. Although the feasibility study did not identify this number of patients, further recruitment to non-responders to the survey invitation will be used to achieve the target number of patients planned for this study. Given the small number of patients targeted for study inclusion and anticipated differences in baseline characteristics between afatinib-treated and patients treated with other systemic therapies, statistical comparisons are not planned. In lieu of a comparative analysis between the afatinib-treated and non-afatinib treated patients are exploratory, the number of patients in each cohort and the precision of estimates are presented (**Table 4**). With up to 70 patients in the afatinib-treated cohort, the standard error (SE) of any bivariate response variable is expected to be between 5.5% and 11.7%.

Table 4. Precision of point estimates around number of patients.

Point Estimate of Proportion	Total Number of eCRFs				
	n=30 (SE)	n=50 (SE)	n=70 (SE)	n=100 (SE)	n=150 (SE)
5%	± 7.8%	± 6.0%	± 5.5%	± 4.3%	± 3.6%
20%	± 14.3%	± 11.1%	± 9.4%	± 7.8%	± 6.4%
30%	± 16.4%	± 12.7%	± 10.7%	± 9.0%	± 7.3%
40%	± 17.5%	± 13.6%	± 11.5%	± 9.6%	± 7.8%
50%	± 17.9%	± 13.9%	± 11.7%	± 9.8%	± 8.0%

9.6 DATA MANAGEMENT

The research team will be responsible for the programming, testing, and hosting of data from submitted eCRFs. Providers will access the eCRF through a secure web-based portal with all data stored on encrypted, password protected, and HIPAA-compliant servers housed within the [redacted] electronic data storage infrastructure. These processes and systems are vetted during the

field-testing procedures. The software used to program the eCRF is the Qualtrics Survey Software. A log of any modifications made to the underlying data as a result of quality control/quality assessment procedures will be maintained. An original copy of the submitted data will always also be maintained. The log will describe any changes made to the database by [redacted]

9.7 DATA ANALYSIS

Demographic and clinical characteristics will be reported by descriptive analyses including counts and frequencies for dichotomous and categorical variables, while measures of centrality (mean, median) and spread (min, max, standard deviation, interquartile range, as appropriate) will be used for continuous variables. These characteristics will be described at the time of initial diagnosis of advanced/metastatic disease and at the time of initiation of each line of therapy received, for the afatinib cohort and separately for the other systemic therapy cohort. No statistical comparisons will be made across these two cohorts in terms of demographic, clinical characteristics, and clinical outcomes.

The calculations for all outcomes (e.g., ORR, DOR, DOCB, TOT, TTP, PFS, OS) are defined in **Table 2** in Section **9.3.2 Outcomes**. For disease response, the point estimate for ORR and associated 95% confidence interval (CI) will be calculated for initial response to index therapy (i.e., afatinib or other systemic therapy) and best response to index therapy, for each cohort. ORR will be reported among subgroups within each of the treatment cohorts, by tumor type and line of therapy. The Kaplan-Meier method will be used to estimate time-to-event outcomes (DOR, DOCB, TOT, TTP, PFS, and OS) to account for any right-censoring (e.g., patient had not discontinued therapy, patient had not progressed, or died). Time-to-event outcomes will be described for each of the two treatment cohorts and in subgroups within the two treatment cohorts, according to solid tumor and line of therapy. All study outcomes will be reported separately for those treated with afatinib monotherapy. In the event an outcome cannot be assessed for a given patient, that patient would be omitted from assessment of that outcome; reason for omission in a given outcome assessment will be reported.

Cumulative incidence, severity, and timing of AEs during the index therapy will be summarized and displayed in number/percentage form for each of the treatment cohorts, separately. All safety endpoints will be analyzed descriptively. AE reporting is summarized in Section **11 Management and Reporting of Adverse Events/Adverse Reactions**.

9.8 QUALITY CONTROL

[redacted] will conduct all data quality assurance and control activities. The following sections outline the data quality assurance and control measures implemented throughout data collection, management, and inspection, prior to constructing a final analytic data file. These procedures are conducted from a programming standpoint (e.g., logic checks built into the data collection tool) via statistical analysis to identify patterns and outliers, and by clinical review to identify implausible data or incongruent data points on a given patient.

9.8.1 eCRF Functionality Testing

Prior to data collection and during the field test, [redacted] will test the eCRF. This quality control process begins with extensive testing of the eCRF to ensure functionality across web-based user environments, looping logic to ensure proper alignment of data-related fields (required responses to certain fields prior to entering data into subsequent field), and other programmatic checks to ensure the reduction of the input of erroneous data (such as specifying maximums for year of birth or initiation of treatment within the dates of the enrollment period). Only data ranges consistent with known clinical parameters will be allowed to be entered into the eCRF.

In addition, the eCRF will be field-tested among four providers to ensure its functionality, the correct interpretation of the questions in relation to the data points of interest, and the length of time required for completion for a single patient. Field-testing includes a [redacted] researcher viewing the screen of the provider completing the eCRF with actual patient data and asking probing questions regarding the functionality, interpretability (variables are aligned with clinical definitions or clinical interpretations), and availability of the variables requested. No data from the pre-testing phase will be used in the analysis for this research. Pre-testing of the eCRF will not commence until receiving IRB approval for the conduct of the study. The pre-test results will be reviewed by BI with [redacted] however, BI will not have access to the individual data collected. Any changes made to the eCRF document as a result of the pre-test will require the resubmission of the eCRF and study protocol to the IRB.

9.8.2 Data Validation

Multiple levels of quality control and quality assessment occur during the study. First, the eCRF includes programmed internal validity checks, including date validation (e.g., date of initiation of index therapy cannot occur before date of initial diagnosis of cancer) and logic that forces providers to respond to required questions. Next, the eCRF will be pre-tested with four clinicians prior to data collection. During this pre-test, [redacted] staff will hold a web-based conference with a selected provider during which the provider will abstract data into the eCRF while [redacted] research staff members monitor and probe the provider regarding the clarity of eCRF data fields. After conducting this pre-test, [redacted] will present findings to BI and suggest revisions to the eCRF as needed. The revised eCRF will be filed with the study IRB.

During data collection, [redacted] clinical research staff review all submitted eCRFs inspecting each for implausible patient clinical profiles based on treatment sequencing, lab and radiology results, or outcomes that are inconsistent with known clinical parameters, or other clinical data that are inconsistent with known standards and outcomes. In addition to review of the submitted data by the clinical research team, the study statistician will conduct an analysis of submitted data to identify any data points inconsistent (outliers) with the study population average. This analysis will include a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns (e.g., TOT). Data points flagged as outliers will be delivered to the clinical research team for further assessment.

Should outliers be discovered, [redacted] clinical research would contact the provider submitting the eCRF for data validation. All providers are informed in their contractual agreement that

follow-up with clinical staff at [redacted] may be required. Participating providers are asked to create a 4-digit unique identifier code per patient that is provided to [redacted] through the eCRF and used for identifying the patient record for validation between [redacted] and the provider. Individual eCRFs will be removed from providers unable to validate a data point, and re-sampling will not occur. All other data will be considered valid provided additional patients from that provider are not selected for random validation.

Random data validation occurs by selecting a random eCRF from each provider submitting a patient. Providers who have been previously verified by [redacted] will not be subject to completion of the random validation. A verified provider is any physician abstractor who has completed at least two of the following: (1) completed and acknowledged our web-based chart data abstraction training in the past 2 years, (2) participated in a chart review pre-test with screen sharing, (3) participated in 2 previous chart review studies in the past 2 years and accurately validated data, and (4) have completed a phone interview with the [redacted] team for data validation. A provider may be verified but still required to answer questions regarding patients with data flagged by [redacted] or [redacted] groups. Providers subject to random validation are asked to complete a 3-data point validation exercise for the patient whereby the provider is given the unique patient identifier but no other information. The provider is asked to re-enter the respective data elements. The three data points may include elements such as the month/year of index treatment initiation, stage at diagnosis, and date of index treatment discontinuation (or date of last treatment/prescription if patient is still on therapy). A provider who fails to validate all data points for a selected patient will be required to submit to further clinical data review. Patients for whom the data are deemed questionable by the research team staff will be excluded; providers will not be compensated for excluded data. No resampling to replace the excluded eCRF will occur. Provider who are nonresponsive to any validation request will have all data submitted excluded from the study.

For all data validation processes, a log of records that undergo statistical and clinical review will be kept, recording the reason a given record was flagged for further follow-up. Should data quality checks and confirmation with providers reveal discrepancies, corrections will be made to the database. These corrections (including whether a record was dropped entirely) will be documented in an audit trail. The number of records undergoing each step of data validation and the number of records corrected or excluded from the final data set will be reported.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The limitations of this approach include provider selection bias, patient selection bias, and the lack of source document verification. Regarding bias, only providers who meet the study eligibility requirements and who volunteer to participate in the research study are known; therefore, the representativeness of the providers to all oncologists in the U.S. cannot be verified directly. Additionally, providers will select the patients meeting study eligibility criteria, so they may not include all potentially eligible patients. As such, the representativeness of the patient sample to all patients in the U.S. or in the population of patients within the [redacted] also cannot be verified. Source document verification cannot be performed by [redacted] however, quality assessment/control procedures to minimize misclassification errors are described in **Section 9.8 – Quality Control.**

1) As an exploratory, retrospective, non-randomized study with up to 70 and up to 50 patients per cohort (respectively), post-hoc propensity score matching cannot be conducted and unadjusted/crude comparisons between the two cohorts cannot be made as underlying demographic/clinical characteristics may exist between the cohort. Therefore, statistical comparisons of outcomes between the two cohorts cannot be made.

2) Not all patient characteristics will be included in the data collection (e.g., income and other variables that may influence provider-prescribing behavior or treatment decisions) and cannot be accounted for in the descriptive analyses.

3) Loss to follow-up during the study period may occur if patients transfer care to other providers and centers. As such, treatments, visits, and outcomes occurring after the date of last visit may be missing.

4) Treatment patterns reflected in the study represent only the practices of providers who have agreed to participate, and may vary from non-responding providers, i.e., those who refused study participation or who were unresponsive to the screening invitation. No data is available to describe non-responders.

5) This study employs purposive sampling that selects providers and patients based on pre-specified selection criteria and hence this may not be representative of all patients diagnosed with *NRG1* gene fusion-positive solid tumors treated with the drugs of interest or representative of all providers treating these types of patients.

6) AEs may be underreported/under-documented in a routine clinical setting as they may occur outside of the office setting and often go unreported compared to what would be expected from a controlled trial or prospective observational study setting. Moreover, providers may not be able to verify that the AEs evaluated in this study meet the criteria as established by CTCAE or other guidelines. Therefore, the frequency of occurrence of AEs cannot be confirmed by this dataset.

7) Although providers will be required to record all patient experiences in the medical charts, there may be some undercounting of events that are unknown to providers due to having occurred outside the office. Thus, the accuracy and completeness of data collected in this study is limited by the quality of data in the patient's medical chart.

9.10 OTHER ASPECTS

N/A

9.11 SUBJECTS

See **Section 9.2 – Provider/Site/Patient Selection** for a description of the patients included in this study.

9.11.1 Cases

N/A

9.11.2 Controls

N/A

9.12 BIAS

Provider and patient selection bias may exist in this study. Provider selection bias will be minimized by only allowing providers to contribute up to 30 patients each. It is expected, however, given the rarity of the patient profile included in this study, that the mean number of patients each provider will contribute is approximately 5 and the total number of providers participating will be greater than 20. Patient selection bias will be minimized to the extent possible by requesting providers complete eCRFs for eligible patients starting chronologically with the earliest patient meeting the criteria and selecting patients consecutively thereafter. To assess the degree of selection made by the participating provider, the total number of patients meeting the study selection criteria will be collected (e.g., 5 patients meet study inclusion/exclusion criteria) will be compared to the number of patients contributed to the study (e.g., 3 patients submitted as CRFs).

In addition, the extent of both provider and patient selection bias is likely minimized by the stringent study selection criteria. Because of the relative rarity of *NRG1* fusion-positive histology, the total prevalence of this patient population is likely small, minimizing potential selection biases.

10 PROTECTION OF HUMAN SUBJECTS

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. All study materials including the research protocol and paper-version of the eCRF will be reviewed by a central IRB prior to any data abstraction including field-testing of the eCRF. A wavier of HIPAA authorization for use of PHI will be requested from the IRB since the following three requirements will be met:

1. The use or disclosure of the PHI involves no more than minimal risk to the individuals, based on the following elements:
   a. An adequate plan to protect identifiers from improper use and disclosure;
   b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and
   c. Adequate written assurances that the PHI will not be reused or redisclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by HIPAA.
2. The research could not be practicably conducted without access to and use of the PHI; and
3. The research could not practicably be conducted without the waiver.

Providers are required to be able to participate in research covered by a central IRB. At all times, patients' PHI will be kept confidential in accordance with HIPAA. The eCRF will not capture any data related to the patient's name, full date of birth, social security number, health insurance plan number, medical record number, or other such PHI. However, date of disease diagnosis, date(s) of treatment(s) administered (including dates of dose changes), date of the development of health states of interest (i.e., SAEs/FAEs, disease progression), and date of death (if available) will be collected in the eCRF. These items are considered PHI under HIPAA. All study results will be reported in aggregate; however, an anonymized patient-level dataset will be delivered to BI at the completion of the analytic cohort build.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a retrospective, non-interventional, non-randomized study using data contained in structured and unstructured areas of the patients EHR previously collected as part of routine clinical care. We are asking chart abstractors (i.e., the patients' treating providers) to abstract information on AEs during afatinib or other systemic therapy. Reporting of these events will be conducted in the manner described in section 11.2.

In addition, reporting requirements and procedures for other AEs identified during the chart review are described in 11.2.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event (AE)

AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Adverse drug reaction (ADR)

An ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from the use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event (SAE)

SAE is defined as any AE that:

- results in death
- is life-threatening
- requires in-patient hospitalization, or
- prolongation of existing hospitalization
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

11.2.1 Collection of AEs

The study design is of non-interventional nature.

The following will be collected and documented on the CRF by the abstracting provider:

- All adverse events (AEs) (serious and non-serious)

All AEs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of AE

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including the pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug.
- The event is known to be caused by or **attributed to the drug class.**
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced.
- **No medically sound alternative etiologies** could explain the event (e.g., pre-existing or concomitant diseases, or co-medications).

- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if the dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g., after five half-lives). Of note, this criterion may not apply to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of AE

Providers will be asked to classify AEs as mild, moderate, or severe based on the medical intervention associated with the AE (see below).

- Mild: mild symptoms; clinical or diagnostic observations only (e.g., lab work); intervention not performed
- Moderate: minimal, local, or noninvasive intervention performed (e.g., administration of fluids)
- Severe: medically significant, ranging from not immediately life-threatening, life-threatening consequences, to death related to AE; (e.g., extensive monitoring, hospitalization or prolongation of hospitalization)

Regardless of the severity of the AE indicated by the provider, the following outcomes will be collected for all AEs, in order to further classify them as serious and/or fatal.

- Resulting in death
- Life-threatening
- Required inpatient hospitalization
- Resulted in persistent or significant disability
- Prolonged existing hospitalization

Pregnancy

In rare cases, pregnancy might have occurred during the study period. Patients who were identified as pregnant while on afatinib will be reviewed. Any drug exposure during pregnancy, which occurred in a female patient or a partner to a male patient will be reported by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed. Otherwise, the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited reporting of AEs and drug exposure during pregnancy

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from start of data extraction once informed consent is signed (if required) onwards until the end of data extraction and provide to BI unique entry point:

Type of Report	Timeline
All **serious ADRs** associated with afatinib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to afatinib *Exemption applies	immediately within 24 hours
All **non-serious ADRs** associated with afatinib	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions, the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax and/or email the NIS AE Form.

*Exemption

Death due to disease progression of the underlying malignancy is a study endpoint and the natural course of the disease. As such, it is exempted from reporting as an SAE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the eCRF only and will not be reported on the NIS AE Form. However, when there is evidence suggesting a causal relationship between afatinib and the progression of the underlying malignancy, the event must be reported as an SAE on the NIS AE Form and on the eCRF.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate CRF pages and the NIS AE form.

Reporting of AEs assessed as related to any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than afatinib according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

AE reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study sponsor (BI) will disseminate the results internally as appropriate and will not release final results until finalization of the study report.

The study sponsor will submit data from this study to appropriate conferences and journals after readout of the study data. Publication planning will involve dissemination of results (both effectiveness and safety/tolerability) from this study in peer-reviewed publications such as abstracts, posters, podium presentations, and manuscripts.

13 REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring *NRG1* Gene Fusions

EU PAS Register® number: N/A
Study reference number (if applicable): CTMS 1200.335

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3.2, 11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1, 9.2, 9.2.1
4.2 Is the planned study population defined in terms of:				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	9.1
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2, 9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	9.9*
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	9.2.1**

Comments:

*General limitation described in Section 9.9 on accuracy of physician-abstracted data.
**While not a comparator, the "other systemic therapy" cohort will provide context in which to assess results among afatinib-treated patients

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2, 9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.12
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2*
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.2*
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

*Where applicable

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 11/May/2020

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

None