CONFIDENTIAL

Protocol for non-interventional studies based on existing data

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Title:	Real-World Effectiveness of Afatinib (Gilotrif) Following Immunotherapy in the Treatment of Metastatic, Squamous Cell Carcinoma of the Lung: A Multi-Site Retrospective Chart Review Study in the U.S.
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
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Research question and objectives:	1) To describe the demographic and clinical characteristics of patients who, after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib in 2L or chemotherapy in 2L (single-agent, doublet, and by specific regimen). 2) To describe time on treatment for patients who, after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib in 2L or chemotherapy in 2L (single-agent, doublet, and by specific regimen). 3) To describe the incidence of severe (grade 3 or higher) irAEs of specific interest (including pneumonitis, colitis, hepatitis, interstitial lung disease, higher indeterminate pulmonary events, death, or discontinuation of therapy due to toxicity) during 2L treatment with afatinib or

	chemotherapy following failure of 1L pembrolizumab in combination with chemotherapy.
Country(-ies) of study:	United States
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MAH contact person:	N/A
Date:	20-SEP-2019

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

1L	First-line
2L	Second-line
3L	Third-line
AE	Adverse Event
CHSS	Cardinal Health Specialty Solutions
CI	Confidence Interval
CRF	Case Report Form
CTR	Clinical Trial Report
DOT	Duration of Treatment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
HIPAA	Health Insurance Portability and Accountability Act
irAE	Immune-related adverse events
IRB	Institutional Review Board
ISF	Investigator Site File
ISPE	International Society for Pharmacoepidemiology
I-O	Immuno-oncology
KM	Kaplan-Meier
NSCLC	Non-small cell lung cancer
OS	Overall survival
OPU	Operative Unit
PD-L1	Programmed death-ligand 1
PHI	Protected Health Information
PFS	Progression-free survival
PS	Performance Status
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SqCC	Squamous cell carcinoma of the lung
Sq NSCLC	Squamous non-small cell lung cancer
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator	[redacted]
Clinical Investigator	
Study Statistician	
Project [redacted]	
Research [redacted]	
Clinical Analyst	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Gi(l)otrif®			
Name of active ingredient: afatinib Antineoplastic agents, tyrosine kinase inhibitors ATC code: L01XE13			
Protocol date: 20 September 2019	**Study number:**	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Real-World Effectiveness of Afatinib (Gilotrif) Following Immunotherapy in the Treatment of Metastatic, Squamous Cell Carcinoma of the Lung: A Multi-Site Retrospective Chart Review Study in the U.S. [redacted]		
Rationale and background:	Pembrolizumab in combination with platinum-doublet chemotherapy is the only U.S. Food and Drug Administration approved, first-line (1L) treatment for patients with squamous non-small cell lung cancer (Sq NSCLC) and is now considered the standard of care based on results from KEYNOTE-407 presented at the American Society of Clinical Oncology annual meeting in June 2018. The effectiveness of afatinib or single-agent chemotherapy as second-line (2L) treatment following exposure to pembrolizumab in combination with platinum-doublet chemotherapy is unknown as no clinical trials have evaluated safety and efficacy of 2L treatments in this setting. This study will use real-world data to examine differences in patient characteristics leading to disease progression and subsequent treatment in 2L with either afatinib or chemotherapy (either single-agent or doublet), evaluate and describe time on treatment between these cohorts, and examine the rate of occurrence of immune-related adverse events (irAEs) during 2L afatinib or chemotherapy.		

Research question and objectives:	1) To describe the demographic and clinical characteristics of patients who, after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib in 2L or chemotherapy in 2L (single-agent, doublet, and by specific regimen). 2) To describe time on treatment for patients who, after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib in 2L or chemotherapy in 2L (single-agent, doublet, and by specific regimen). 3) To describe the incidence of severe (grade 3 or higher) irAEs of specific interest (including pneumonitis, colitis, hepatitis, interstitial lung disease, higher indeterminate pulmonary events, death, or discontinuation of therapy due to toxicity) during 2L treatment with afatinib or chemotherapy following failure of 1L pembrolizumab in combination with chemotherapy.
Study design:	This is a non-interventional, multi-site cohort study based on existing data from electronic medical records of patients with advanced or metastatic Sq NSCLC treated with pembrolizumab in combination with platinum doublet chemotherapy as 1L treatment followed by either afatinib as 2L treatment or chemotherapy as 2L treatment.
Population:	U.S.-based community oncologists will select patients meeting the study eligibility criteria as describe below. <u>Inclusion Criteria:</u> • Diagnosis of squamous or mixed histology non-small cell lung cancer. • Treated with pembrolizumab in combination with platinum-based chemotherapy as initial therapy for advanced or metastatic disease (stage IIIB or IV). o First cycle of pembrolizumab containing therapy received after 06/01/2018. o Permanently discontinued 1L pembrolizumab containing treatment. • Initiated second-line treatment at least 3 months prior to data collection with either: o Afatinib o Any chemotherapy • Age ≥ 18 years <u>Exclusion Criteria:</u> • Received pembrolizumab in combination with platinum-based chemotherapy as part of an interventional clinical trial.
Variables:	Primary Outcome(s): 1) Demographics, clinical characteristics and treatment history of patients who receive 2L afatinib or 2L chemotherapy 2) Time on treatment in 2L with afatinib and time on treatment in 2L with chemotherapy 3) Incidence rates of severe (grade 3 or higher) irAEs of specific interest during 2L treatment (including pneumonitis, colitis, hepatitis, interstitial lung disease, indeterminate pulmonary events, death or discontinuation of 2L therapy due to toxicity)

Data sources:	Data will be collected from patients' medical records and recorded in an electronic case report form by the patient's treating provider. Providers will be recruited to participate from a list of over 7,000 oncologists, haematologists and urologists from across the US.
Study size:	Total enrolled: approximately 200 patients including 100 patients treated in 2L with afatinib and 100 patients treated in 2L with chemotherapy.
Data analysis:	Descriptive analysis of demographics, clinical characteristics, and treatment history of patients treated in 2L with afatinib and those treated in 2L chemotherapy. Time on treatment will be described in each 2L cohort (with no comparisons made) using the Kaplan-Meier method, and the median, along with two-sided 95% confidence intervals, and 3-, 6-, 9- and 12-month rates of discontinuation will be reported. Time on treatment is defined in months as the interval from the start of 2L treatment until the end of 2L treatment or death date by any cause. Incidence rates of severe irAEs of specific interest during 2L afatinib treatment or 2L chemotherapy will be estimated as the number of events divided by the total person-years of follow-up. Additionally, the incidence rates among patients who completed 2L therapy will be reported.
Milestones:	Start of data collection January 2020 End of data collection in March 2020* Study progress report in February 2020 Final report of study results expected in May 2020 *The results of this descriptive study may be used to inform a follow-up comparative study for which additional data collection time may be required.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	13 January 2020
End of data collection	10 February 2020
Study progress report/interim results*	28 February 2020
End of data collection (quality control assessment and update completed)	27 March 2020
Final report of study results	29 May 2020

* The results of this descriptive study may be used to inform a follow-up comparative study for which additional data collection time may be required. The protocol may be amended at that time.

7. RATIONALE AND BACKGROUND

Squamous cell carcinoma (SqCC) of the lung accounts for 20-30% of non-small cell lung cancer (NSCLC) cases.[1] The underlying molecular pathogenesis of SqCC of the lung is less well understood than other histologies.[2] Historically, the standard of care in first-line (1L) has been platinum-doublet chemotherapy which provides a response rate of approximately 20% and a median overall survival (OS) of less than 8 months.[3,4] Upon disease progression, three targeted agents, afatinib, erlotinib, and ramucirumab, are approved as second-line (2L) therapy. Afatinib (Gilotrif) is an irreversible kinase inhibitor of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4). Aberrations in the ErbB/HER family have been found in approximately 22% of patients with advanced, squamous non-small cell lung cancer (NSCLC).[5] Afatinib was approved in 2016 for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy based on the findings of the LUX-Lung-8 trial that demonstrated improved overall survival (OS) and progression-free survival (PFS) in comparison to those who received erlotinib in 2L.[6]

In October 2018 pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was approved by the U.S. Food and Drug Administration for 1L treatment of metastatic SqCC of the lung. In the Keynote-407 trial, the median OS in the pembrolizumab/chemotherapy combination arm was 15.9 months compared to 11.3 months in the placebo-combination group (with consistent results regardless of PD-L1 expression level).[7] Results of the Keynote-407 trial were initially presented at the American Society of Clinical Oncology (ASCO) annual meeting in June 2018.[8] Subsequently the National Comprehensive Cancer Network guidelines for 1L treatment of squamous NSCLC were updated with the combination receiving a category 2A recommendation establishing a new 1L standard of care within one month of the ASCO presentation.[9] Pembrolizumab in combination with chemotherapy remains the only approved 1L treatment at this time.

Randomized controlled trials of afatinib following any 1L immuno-oncology (I-O) treatment for metastatic SqCC of the lung have yet to be undertaken. However, preliminary feasibility and market research have shown utilization of afatinib as 2L and third-line (3L) therapy following 1L I-O monotherapy or 1L I-O in combination with chemotherapy. As such, there is a significant need to describe the patient types and effectiveness of afatinib, as 2L, following 1L I-O plus chemotherapy, given that LUX-Lung-8 was specific to afatinib following initial chemotherapy only. Moreover, while IO therapy and EGFR tyrosine-kinase inhibitors have demonstrably different mechanisms of action severe immune-related adverse events (irAEs) have occurred in patients who have received sequential I-O to EGFR therapy or concurrent IO/EGFR combination therapy.[10-11] These events include grade 3 or higher pneumonitis, colitis, hepatitis, interstitial lung disease, or indeterminate pulmonary events. Therefore, real-world data from patients treated in community oncology clinics in the U.S. is needed to further examine the incidence and outcomes of these severe irAEs of specific interest.

8. RESEARCH QUESTION AND OBJECTIVES

With a new 1L standard of care for patients with SqCC of the lung, the profile and outcomes for patients who progress and receive afatinib as 2L therapy have not been characterized. The proposed research study will aim to answer the following key questions:

1) What are the demographic and clinical differences between patients who received afatinib following pembrolizumab combination with chemotherapy (e.g. afatinib as 2L) versus those who receive 2L chemotherapy and are never treated with afatinib?
2) What is the real-world time on treatment for patients who receive afatinib after failure following 1L pembrolizumab combination with chemotherapy? What is the time on treatment for those receiving 2L chemotherapy after prior pembrolizumab plus chemotherapy?
3) What are the real-world rates of severe irAEs during 2L treatment with afatinib or chemotherapy following 1L pembrolizumab plus chemotherapy?

To address these research questions the following objectives are proposed for this retrospective, observational study:

1) To describe the demographic and clinical characteristics of patients, who after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib in 2L or chemotherapy in 2L (single-agent, doublet, and by specific regimen).
2) To describe time on treatment in 2L for patients who, after failure of 1L pembrolizumab in combination with chemotherapy, received either afatinib or chemotherapy in 2L (single-agent, doublet, and by specific regimen).
3) To describe the incidence of severe (grade 3 or higher) irAEs of specific interest (including pneumonitis, colitis, hepatitis, interstitial lung disease, higher indeterminate pulmonary events, death, or discontinuation of therapy due to toxicity) during 2L treatment with afatinib or chemotherapy following failure of 1L pembrolizumab in combination with chemotherapy.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, retrospective, multi-site cohort study based on existing data from medical records of patients with metastatic SqCC of the lung treated with pembrolizumab in combination with platinum doublet chemotherapy as 1L treatment followed by either afatinib as 2L treatment or chemotherapy as 2L treatment. Data collection will begin after December 2019 and complete in February 2020. All patients are required to have initiated 1L pembrolizumab and platinum combination chemotherapy after 01 June 2018 (post release of the Keynote-407 trial results at ASCO Annual Meeting), discontinued 1L therapy, and initiated 2L treatment at least 3 months prior to the date of data collection. As such the maximum follow-up period for patients is approximately 15 months. The index date is the date of initiation of 2L therapy with either afatinib or chemotherapy. The proposed research design allows for nearly real-time data collection with no lag, abstraction of detailed clinical and treatment-related data points, and determination of the date of death.

In total, approximately 200 patients will be selected for this study of whom approximately 100 are 2L afatinib treated and 100 who are treated in 2L with chemotherapy. The objectives of this study are to describe patient demographics and clinical characteristics at diagnosis and discontinuation of 1L therapy for each cohort. As a retrospective, descriptive study no direct comparisons between cohorts will be made. In addition to describe the patient cohort characteristics time on treatment will be estimated. Time on treatment is defined as the interval from the start of 2L treatment until the end of 2L treatment or death date by any cause. Finally, the frequency and timing of irAEs during afatinib treatment will be assessed. The results of this descriptive study may be used to inform a follow-up comparative study for which additional data collection time may be required.

The limitations of this approach include provider selection bias, patient selection bias, and the inability to perform source document verification. As only providers who meet the study eligibility requirements and who volunteer to participate in the research study are known the representativeness of the providers to all oncologists in the U.S. cannot be verified directly. Second, providers will select the patients meeting the study eligibility criteria and providers may not include all patients who could be eligible. The representativeness of the patient sample to all patients in the U.S. cannot be verified. Source document verification cannot be performed, however quality assessment/quality control procedure to minimize misclassification errors are described in **Section 9.8 – Quality Control.**

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 is capped at 10. Data will be collected through an electronic case report form (eCRF) completed by the patient's providers volunteering 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 is assumed to take approximately 1 hour per patient.

Recruitment of providers will be conducted electronically. Providers who responded to an initial feasibility request who reported treating potentially eligible patients will be contacted and invited to participate. Recruitment to fill the 200 patient quota will run for 4 weeks from the data of recruitment launch. During that time the per cohort quotas will be electronically monitored to ensure that the final samples are balanced with 100 patients in each arm. 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 100.

Providers will be asked to identify all eligible patients, and chronologically, starting with the earliest index date, select consecutive patients meeting the eligibility criteria and complete data abstraction. The eCRF is structured to allow data collection regarding patient clinical history at the time of initial diagnosis of lung cancer, initiation of 1L therapy, initiation of 2L therapy, treatment regimens (including dates of starts, stops, interruptions) during 1L and 2L, dates of disease progression, severe irAEs of specific interest, subsequent regimens used in 3L and beyond, and date of death. For severe irAEs the physician will be provided with information regarding the CTCAE definition of each of the specific events of interest. The provider will make the final determination as to whether the event occurred (e.g. distinction between severe diarrhea and colitis) and the attribution of the event or substantiation of either the event grade or attribution cannot be completed. Events are considered a bonafide irAE if documented as immune-mediated in real time by the primary oncologist involved in the care of the patient and supported by radiologic and/or pathologic evidence. Adverse events that were possibly immune-mediated but had alternative or mixed etiologies will be termed "indeterminate irAEs" and considered separately.

9.2.1 Provider/Site/Patient Selection

Providers

Provider will be eligible to participate in this research study who meet the following criteria:

1) Board certified hematologist/oncologist.
2) Have treated/are treating at least two patients with Sq NSCLC in 1L with I-O/platinum chemotherapy combination.
3) Have treated at least two NSCLC patients with afatinib since 2016.
4) Able to participate in research covered by a central institutional review board (IRB).

Patients

Providers will select patients meeting the study eligibility criteria as describe below. Providers will be asked to select eligible patients chronologically, starting with the first patient who first initiated 2L afatinib or chemotherapy on or after 06/01/2018 but at least 3 months prior to data collection, and then randomly from that point forward until they have submitted their maximum number of patients or no further patients are evaluable.

Inclusion Criteria:

- Diagnosis of squamous or mixed histology non-small cell lung cancer.
- Treated with pembrolizumab in combination with platinum-based chemotherapy as initial therapy for advanced or metastatic disease (stage IIIB or IV).
    - First cycle of pembrolizumab received after 06/01/2018

  - Permanently discontinued 1L pembrolizumab treatment.
- Initiated second-line treatment at least 3 months prior to the date of data collection. with either :
  - Afatinib
  - Any chemotherapy
- Age ≥ 18 years

Exclusion Criteria:

- Received pembrolizumab in combination with platinum-based chemotherapy as part of an interventional clinical trial.

Patients who were treated with pembrolizumab in combination with platinum-based chemotherapy as part of a clinical trial will not be selected to ensure the non-interventional nature of the study design and that no differential care was received.

9.3 VARIABLES

The patients treated/managing provider is the chart data abstractor in this study. The provider will review the patients EHR and abstract the data points described below from the EHR into the eCRF. Source documents (e.g. the structured fields of the EMR database) will not be provided to Cardinal Health. All the variables described below will be transformed into a series of questions the provider will answer based on the data in the EHR. The data points described below will be collected for each of the study cohorts (2L afatinib and 2L other chemotherapy).

Providers

- Provider characteristics: practice location, practice size, urban versus rural location, years in practice, number of Sq NSCLC patients treated/treating, medical specialty

Patient Demographics/Clinical Characteristics

- Patient demographics: sex, year of birth, payer at initiation of 2L, region of primary residence, race/ethnicity, Hispanic
- Smoking history at time of diagnosis: never, former, current
- Date of initial lung cancer diagnosis, date of diagnosis of advanced/metastatic disease
- NSCLC histology
- Stage (pathological and clinical) at initial diagnosis
- Molecular/genetic mutations reported: Erb1/Her2 (ErbB2)/3 (ErbB3)/4 (ErbB4), PD-1(L1), if available
  - Method of testing (e.g., NGS, etc.)
- ECOG-PS at 1L initiation, 2L initiation
- Clinically relevant comorbidities including Charlson components at initiation of 1L, 2L
- Sites of metastatic disease at 1L, 2L
  - Counts of metastatic sites at 1L, 2L

Patient Treatment Regimens

- Surgical resection of tumor and date
- Receipt of radiation therapy overall and by line of therapy

- Treatment regimens received as neoadjuvant, adjuvant, maintenance therapy, 1L, 2L, and 3L or greater
    - Dates of initiation
    - Dates of discontinuation
    - Total number of cycles received
    - Starting dose/ ending dose
    - Days of supply of last prescription for afatinib during the follow-up period
- Dose reduction(s)/number, dose interruption(s)/ number during 1L, 2L
- Rationale for discontinuation of 1L, 2L, 3L or greater
    - Progression, toxicity/adverse event, patient choice, death, other

If death cited as rationale for discontinuation then provider will abstract data related to date of death, cause of death – see bottom of next section. Death during treatment and toxicity/AE as the rationale for discontinuation of 2L therapy is considered a severe AE of specific interest for this study.

Patient Clinical/ Follow-up Outcomes

- Diagnosis, time, grade, and attribution (treatment-related or not per provider interpretation) of any of the following severe (grade 3 or greater) irAEs during 1L/2L
    - Pneumonitis, colitis, hepatitis, interstitial lung disease, or indeterminate pulmonary event
- Hospitalization(s)/number during 1L, 2L
- Emergency department visit/ number during 1L, 2L
- Date of disease progression in 1L, 2L, 3L and greater (provider reported and/or radiographically confirmed)
    - Attribution of disease progression/death due to treatment
- Date of last clinic visit
- Referral to hospice/ date
- Date of death
    - Cause of death: cancer related, non-cancer related

Providers will only be queried if the severe irAE's (grade 3 or higher) listed above, occurred during therapy. No other severe irAEs will be captured in structured fields of the eCRF. Should the provider notify Cardinal Health of another adverse drug reaction/adverse event, Cardinal Health will follow the procedures outlined in Section 11 for reporting.

9.3.1 Exposures

- Pembrolizumab in combination with platinum-based doublet chemotherapy
- Afatinib as 2L therapy following discontinuation of pembrolizumab in combination with platinum-based doublet chemotherapy
- Any chemotherapy as 2L therapy following discontinuation of pembrolizumab in combination with platinum-based doublet chemotherapy

9.3.2 Outcomes

9.3.2.1 Primary outcomes

To describe the demographic and clinical characteristics of and between patients receiving 2L afatinib or 2L chemotherapy all variables listed as Patient Demographics /Clinical Characteristics will be reported in terms of frequencies and proportions for categorical variable and means or medians (as appropriate) for continuous variables.

Time on treatment with afatinib or chemotherapy during 2L. Time on treatment is defined as the interval from the start of 2L treatment until the end of 2L treatment or death date by any cause.

The incidence of severe irAE of specific interest during 2L treatment will be reported as the proportion of patients experiencing the event among all patients who completed 2L therapy (e.g. discontinued) and as an incidence rate when including all patients in the 2L afatinib or chemotherapy cohort. Any discontinuation of 2L therapy due to toxicity or death will be reported in aggregate as a frequency/proportion.

9.3.2.2 Secondary outcomes

NA

[redacted]

9.3.3 Covariates

As a descriptive, retrospective study no formal comparisons between 2L afatinib and chemotherapy-treated patients will be made. For evaluation of the incidence of irAEs during afatinib treatment covariates of interest include patients' history or irAE during 1L treatment along with the previously described demographics, clinical characteristics, and patient treatment regimens.

9.4 DATA SOURCES

Data will be collected from patients' medical records and recorded in the eCRF. Providers will be recruited to participate from a list of over 7,000 oncologists, haematologists and urologists from across the US, with varying levels of time in practice, from practices both within and outside of group purchasing organizations.

Provider recruitment and patient identification activities are conducted over the span of 4 weeks from the date of recruitment launch. During this 4-week interval, providers who responded to a feasibility assessment conducted prior to the launch of the study will be invited to participate first followed by recruitment from the maximum list of providers as needed. Should recruitment from the larger network be required, the research team will

identify providers caring for patients with a diagnosis of lung cancer based on ICD-9/10-CM diagnosis codes through the overlay of an internal administrative claims database with the provider list. Should this recruitment strategy not complete recruitment, the research team will invite all remaining providers known via electronic mail to participate in the research.

9.4.1 Source Documents

Source documents will not be reviewed by the study research team for validation of the data points. Providers who elect to participate will abstract all relevant data from the patients' medical record into the eCRF. See **Section 9.8 – Quality Control** for details describing the approach to data validation in the absence of source document verification.

9.4.2 Dataset and Records

Individual eCRF's will not be provided to the study sponsor for review. An analytical, patient-level dataset will not be provided to the study sponsor. The research team will retain the source documents according to the contract between the research team and the study sponsor.

9.5 STUDY SIZE

A priori the study size was determined to be 200 patients with 100 patients each included in the 2L afatinib and 2L chemotherapy cohorts. The sample size was determined based on resources available for provider honoraria payment and the number of potentially eligible patients that were identified during a feasibility assessment. As a descriptive study with no formal hypothesis tests or comparisons no formal sample size/power analysis has been conducted. The primary sample size consideration for this study is the ability to measure the time on treatment in 2L and the precision of that point estimate. The LUX-Lung 8 trial demonstrated a median PFS of 2.4 months in the afatinib treated patients and 1.9 months in the erlotinib treated patients. Based on the planned data collection period we anticipate that sufficient patients to measure the 2L PFS will be available.

9.6 DATA MANAGEMENT

All study data will be entered 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 electronic medical record (EMR) based on the journey of the patient through the course of their 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).

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 Cardinal Health 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.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Demographic and clinical characteristics of the 2L afatinib treated and 2L chemotherapy treated cohorts will be summarized using 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 techniques will also be used to describe the occurrence of selected toxicities during treatment in cohorts according the length of follow-up for the patient. The frequency of occurrence of these events will only be reported in total among those patients who had discontinued afatinib therapy. Events are considered a bonafide irAE if documented as immune-mediated in real time by the primary oncologist involved in the care of the patient and supported by radiologic and/or pathologic evidence. Adverse events that were possibly immune-mediated but had alternative or mixed etiologies will be termed “indeterminate irAEs” and considered separately. In addition, the incidence rate of each toxicity will be estimated using the length of follow-up or time on treatment during specific lines of therapy. All analyses will be conducted in SAS v9.4.

The primary outcome to be measured in this study is the time on treatment in 2L for the afatinib and 2L chemotherapy cohorts. Time on treatment is defined in months as the interval from the start of 2L treatment until the end of 2L treatment or death date by any cause. The end of 2L treatment is defined as the date of last treatment order for afatinib plus the days of supply on the last known treatment order up to the date of data collection (but not exceeding). The Kaplan-Meier (KM) method will be used to estimate the median and 95% confidence interval for time on treatment. In addition the proportion of patients still receiving 2L afatinib or 2L chemotherapy at 3, 6, 9, and 12 months post 2L initiation will be reported from the results of the KM analysis. Patients who are considered on therapy at the time of last visit will be censored on the last treatment date as previously described. Patients who have discontinued treatment for any reason will be considered events and the date of the event will be captured as previously described.

9.8 QUALITY CONTROL

9.8.1 eCRF Functionality Testing

Prior to data collection, during the field test, or actual study launch, Cardinal Health 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 first-line treatment within the dates of the enrollment period). Data ranges consistent with known clinical parameters will only be allowed to be entered into the eCRF.

In addition, the eCRF will be field-tested among 4 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 Cardinal Health 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 the study sponsor with Cardinal Health staff, however, the study sponsor 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

During data collection Cardinal Health clinical research staff review all submitted eCRFs for quality control. The CHS Cardinal Health S clinical research team will inspect each submitted eCRF for implausible dates (i.e., date of death prior to last date of treatment), non-standard treatments (e.g., treatment regimens unknown to be used for the cancer under study), lab and radiology results which 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. DOT). Data points flagged as outliers will be delivered to the clinical research team.

Should outliers be discovered, Cardinal Health clinical research will contact the provider submitting the eCRF for data validation. All providers are informed in their contractual agreement that follow-up with clinical staff at Cardinal Health may be required. Participating providers are asked to create a 4-digit unique identifier code per patient that is provided to Cardinal Health through the eCRF and used for identifying the patient record for validation between Cardinal Health and the provider. Individual eCRFs that cannot be validated will be removed from the study dataset; a provider unable to validate a data point will not be compensated for the patient record that was removed and re-sampling will not occurr without an amendment to the statement of work. 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 previoulsy verified by Cardinal Health 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) particpated 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 Cardinal Health team for data validation. A provider may be verfiied but still required to answer questions regarding patients with data flagged by Cardinal Health research operationa or research analytics 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 data elements. The 3 data points may include: month/year of 2L treatment initiation, stage at diagnosis, and date of 2L treatment discontinuation (or date of last treatment/prescription if patient 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 researh team staff will be excluded; providers will not be compensated for exlcuded data. No resampling to replace the excluded eCRF will occur. Provider who are non-responsive to any validation request will have all data submitted excluded from the study.

Should data quality checks and confirmation with providers reveal discrepancies corrections will be made to the database. These corrections will be documented in an audit trail.

9.9 LIMITATIONS OF THE RESEARCH METHODS

There are several limitations to this research which should be noted.

1) As an exploratory, retrospective, non-randomized study with a sample size of 100 patients per cohort post-hoc propensity score matching cannot be conducted and comparisons between the two cohorts cannot be made as underlying demographic/clinical characteristics may exist between the cohort. Therefore, no numerical comparisons of endpoints between the two cohorts should be made at this time.

2) Not all patient characteristics will be included in the data collection (e.g., income and other variables which may influence physician-prescribing behavior or treatment decisions) and cannot be accounted for in the descriptive or multivariate 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 physicians who have agreed to participate, and may vary from non-responding physicians, 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 physicians and patients based on pre-specified selection criteria and hence this may not be representative of all patients diagnosed with NSCLC treated with the drugs of interest or representative of all physicians treating these types of patients. In particular we require that patients have discontinued 1L treatment and received 2L therapy therefore any long-term responders to 1L therapy are excluded. Furthermore, by requiring that patients initiated 2L therapy at least 3 months prior to data cut-off we may bias our results in favor of longer 2L treatment durations as it is likely that early discontinuers may not be selected. We have attempted to mitigate this by asking for consecutive patients starting with the earliest and capping the maximum number of patient charts submitted per provider to 10.

6) Adverse events 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 the severe irAEs evaluated in this study meet the criteria as established by CTCAE or other bodies. Therefore, the frequency of occurrence of severe irAEs signal cannot be confirmed by this dataset.

7) Although physicians will be required to record all patient experiences in the medical charts, there may be some undercounting of events that are unknown to physicians which 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

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

9.11 SUBJECTS

Please see **Section 9.2 – Provider/Site/Patient Selection** for a description of the patients to be studied in this research.

9.11.1 Cases

NA

9.11.2 Controls

NA

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 10 patients each therefore the minimum number of providers participating is 20. 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 30. 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.

In addition the extent of both provider and patient selection bias is likely minimized by the stringent study selection criteria. Because of the relatively recent approval granted to pembrolizumab in combination with platinum-doublet chemotherapy as initial treatment for Sq NSCLC, the relative rarity of squamous as opposed to non-squamous NSCLC histology, and the requirement that all patients had initiated 2L therapy the total prevalence of this patient population is likely small minimizing potential selection biases.

10. PROTECTION OF HUMAN SUBJECTS

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. Providers are required to be able to participate in research covered by a central IRB. At all times, patients' protected health information (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. an adverse event, disease progression), and date of death (if available) will be collected in the eCRF. These items are considered PHI under HIPAA. At no time will the study sponsor be provided PHI in the form of a dataset or otherwise; all study results will be reported in aggregate.

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 physician) to abstract information regarding severe (grade 3 or higher) irAEs of specific interest (including pneumonitis, colitis, hepatitis, interstitial lung disease, higher indeterminate pulmonary events, death, or discontinuation of therapy due to toxicity) during 1L and 2L for both patients treated with afatinib in 2L and those treated with chemotherapy in 2L. Providers/abstractors will be asked only if these specific immune related events occurred. Reporting of these events will be conducted in the manner described in section 11.2. Events are considered a bonafide irAE if documented as immune-mediated in real time by the primary oncologist involved in the care of the patient and supported by radiologic and/or pathologic evidence. Adverse events that were possibly immune-mediated but had alternative or mixed etiologies will be termed "indeterminate irAEs" and considered separately.

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

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

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 findng), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction 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 authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event

SAE is defined as any AE which

- results in death
- is life-threatening
- requires in-patient hospitalisation, or prolongation of existing hospitalisation
- 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 hospitalisation but may jeopardise 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 hospitalisation 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.

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, and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the afatinib. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from start of data extraction once informed consent is signed (if required) onwards until the end of data extraction:

- all adverse drug reaction (ADRs) (serious and non-serious),

- all AEs with fatal outcome,

The investigator carefully assesses whether an AE constitutes an ADR using the information below. **Causal relationship of adverse event**

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** that 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, taking into account the pharmacological properties of the compound (e.g., after 5 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 adverse event

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria *version 5.0* in the eCRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken afatinib, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or a partner to a male subject to the Sponsor 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 related AEs associated with 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 Authorisation Holder （MAH） according to local and international regulatory requirements.

Exemptions are described in section 11.2, if applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study sponsor will disseminate the results internally as appropriate. The study sponsor will not release final results until finalization of the study report. The study sponsor will plan to publish the results (both effectiveness and safety/tolerability) from this study peer-review publications such as abstracts, posters, podium presentations and manuscripts.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

NA

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

None