Non-Interventional Study Protocol
A7471067

ARIA: Real-world utilization and outcomes with dacomitinib first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer among Asian patients – A multi-center chart review

Statistical Analysis Plan
(SAP)

Version: 2.0

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Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
AIDS	acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ARCHER 1050	Randomised, open-label, phase 3 trial of dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer
ARIA	Advanced NSCLC Real World Study of DacomItinib in Asian patients
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
CAT	categorical
CCI	Charlson Comorbidity Index
CDE	Center for Drug Evaluation
CI	confidence interval
CNS	central nervous system
CON	continuous
CR	complete response
CRF	case report form
CSA	clinical study agreement
DCT	data collection tool
DMP	data management plan
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ErbB	Erb-b2 receptor tyrosine kinases
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
ICD	informed consent document
IEC	Independent Ethics Committee
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous
LAR	legally acceptable representative
MedDRA	Medical Dictionary for Regulatory Activities

NA	not applicable
NCCN	National Comprehensive Cancer Network
NI	non-interventional
NIS	Non-interventional study
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
OH (CCO)	Ontario Health (Cancer Care Ontario)
OS	overall survival
PAC	Post-Approval Commitment
PASS	Post-Authorization Safety Study
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria In Solid Tumors
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SDV	source data verification
SMP	study monitoring plan
SOC	System Organ Class
STD	standard deviation
TKI	tyrosine kinase inhibitor
TNM	Tumor, Node and Metastasis
TTE	time-to-event
TTF	time-to-treatment failure
U.S.	United States
WHO	World Health Organization
YRR	Your Reporting Responsibilities

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Below is a summary of amendments made to version 1.0:

Date	Section	Amendment
25 July 2024	5.3.2 Derivation rules for time-to-event outcomes	Event and censoring rules have been further specified for outcomes including OS, PFS, and TTF.
25 July 2024	6 Handling of missing values	Imputation method has been added for handling of missing dates.

2 INTRODUCTION

Dacomitinib, a second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was approved by the United States (U.S.) Food and Drug Administration (FDA) as treatment for advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. In the ARCHER 1050 randomized trial, a statistically significant improvement in progression-free survival (PFS) was observed with dacomitinib compared to gefitinib.

There is currently a paucity of information on the real-world utilization of dacomitinib and associated clinical outcomes among Asian patients with EGFR mutation-positive advanced NSCLC. Understanding the characteristics, drug utilization and outcomes of these patients prescribed with dacomitinib represent an important step towards addressing the existing knowledge gaps.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the National Medical Products Administration (NMPA)'s Center for Drug Evaluation (CDE) of China.

2.1 STUDY DESIGN

This is a longitudinal, multi-center cohort study with mixed prospective and retrospective data collection (Figure 1). As this is an observational real-world study, no investigative drug or intervention will be administered as part of study participation. Physicians will provide treatment based on their routine practices and in the best interests of the patients under their care.

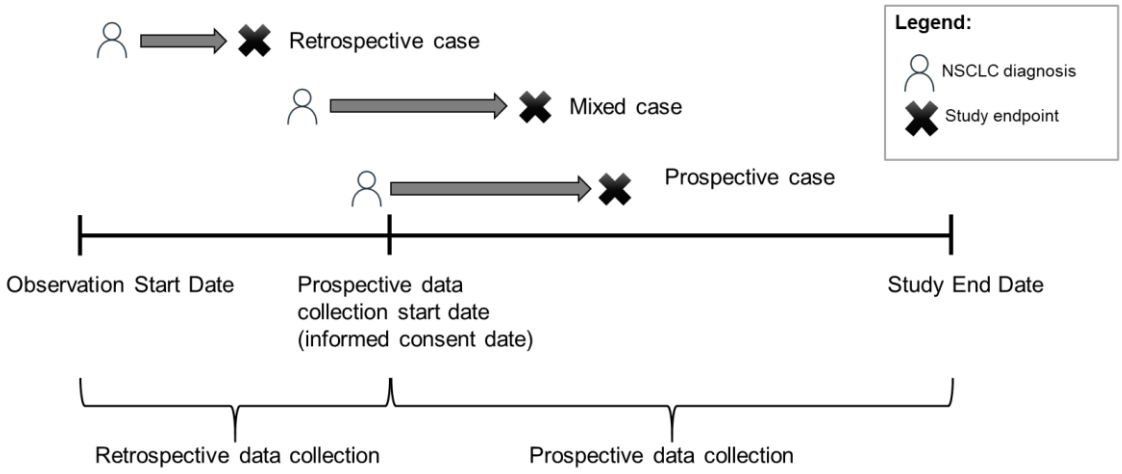
A study patient is defined as an adult (aged ≥18 years) with EGFR mutation-positive advanced NSCLC treated with dacomitinib as first-line therapy within the study observation period. Patients could be given dacomitinib treatment during the pre-marketing authorization compassionate use program in India and Malaysia, and/after it is commercially available in China, India and Malaysia.

All patients with documented NSCLC diagnosis or record of dacomitinib use will be screened for study eligibility. Data will be collected from the eligible patients from the date of advanced NSCLC diagnosis to the study endpoint ie, date of death, lost to follow-up, withdrawal of consent or end of study (observation period), whichever occurs first.

Clinical data including characteristics, treatment and outcomes will be collected. Baseline characteristics are based on the last non-missing measurement collected prior to dacomitinib initiation. Prospective patient

identification will start from the study initialization to enrolment end date. After the enrolment period, only follow up data will be collected and there will be no identification of new prospective patients. The enrolment period may be shortened or extended depending on whether the target number of participants can be included into the study within the stipulated time. The period for retrospective patient identification and retrospective data collection will be from observation start date to prospective data collection start date date.

Figure 1. Schematic Diagram of Study Design and Planned Data Collection Approaches for Eligible Patients



Three different approaches of data collection are further described below:

- Enrolled patients who started dacomitinib before the prospective data collection start date (or informed consent date), and had last visit at or before the data collection start date are retrospective patients.
- Enrolled patients who started dacomitinib before the prospective data collection start date (or informed consent date), and have visit after the data collection start date are mixed patients.
- Enrolled patients who started dacomitinib at the prospective data collection start date (or informed consent date), and have visit after the data collection start date are prospective patients.

Study population

Approximately fifteen tertiary cancer treating hospitals in China, India and Malaysia are anticipated to be participating in this study. The total target number of NSCLC study patients is 300 for this study. For China, the target number is at least 200 patients with a maximum number of 290 patients.

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Adult (aged ≥18 years) with histology-confirmed advanced NSCLC (TNM stage IIIB-IV);
2. Presence of any EGFR-activating mutation (exon 19 deletion or exon 21 L858R substitution) or other uncommon EGFR mutations prior to anti-cancer treatment;
3. Initiating dacomitinib as first-line treatment for advanced NSCLC after confirmation of EGFR-mutation status (ie, no prior treatment with other EGFR TKI or systemic therapy);
4. Received dacomitinib after the following dates (which mark the marketing authorization date in China, or initiation of the compassionate use program in Malaysia and India);
    a. Patients from China: July 1st 2019;

b. Patients from Malaysia and India: August 1st 2018

5. Initiated dacomitinib no later than 20 months before end of data collection (to allow minimum of 20 months follow-up from dacomitinib initiation);

6. Had at least one follow-up visit after dacomitinib initiation unless there was a documented death in the patient records before a follow-up visit.

In addition, for prospective and mixed patients, there should be evidence of a personally signed and dated informed consent document (ICD) indicating that the patient (or a legally acceptable representative, LAR) has been informed of all pertinent aspects of the study. This is subjected to obtaining an informed consent waiver for retrospective patients from the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

Patients meeting any of the following criteria will not be included in the study:

1) Enrolled in any interventional clinical study or trial at time of study inclusion (however, patients enrolled in non-interventional, real world study may still be included).

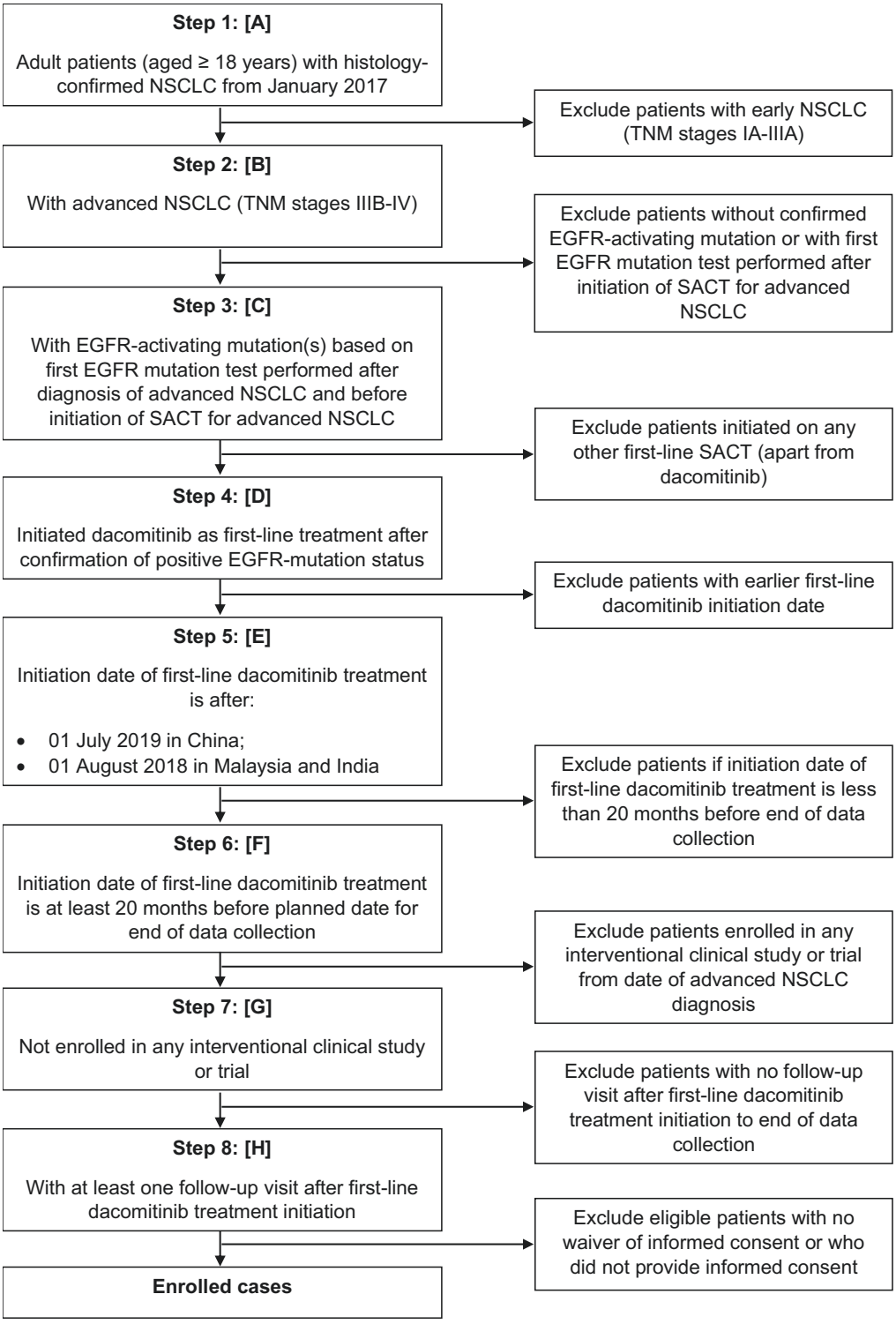
The flow diagram (Figure 2) provides a schematic overview of the method used to identify and select the primary cohort for analysis. The steps are further described in Table 1.

Table 1. Description of Steps in Patient Selection

Step	Description	Ref. in Figure 2
1	Patients aged at least 18 years at date of histology-confirmed NSCLC will be selected from the study observation period.	[A]
2	NSCLC patients with advanced disease will be selected based on TNM staging (IIIB-IV). TNM staging should be determined based on the American Joint Committee on Cancer (AJCC) 8th edition cancer staging manual.[1]	[B]
3	Advanced NSCLC patients with EGFR-activating mutation(s) will be selected at this step. This implies that patients should have the first EGFR mutation test performed at or after diagnosis of advanced NSCLC and before initiation of first-line treatment. First-line treatment will be defined as the first systemic anti-cancer therapy (SACT) for advanced NSCLC.	[C]
4	In this step, EGFR mutation-positive advanced NSCLC patients who have initiated dacomitinib as first-line treatment will be selected. Patients initiated on any other first-line SACT will be excluded.	[D]
5	Initiation date of first-line dacomitinib treatment should be after July 1st 2019 for China, August 1st 2018 for Malaysia and India. Patients with earlier first-line dacomitinib initiation date will be excluded.	[E]

6	Initiation date of first-line dacomitinib treatment should be at least 20 months before planned date for end of data collection. This is to ensure adequate length of follow-up for enrolled patients. Depending on the dacomitinib initiation date for the last enrolled patient, the study end date for data collection may need to be changed accordingly.	[F]
7	Only patients not enrolled in any interventional clinical study or trial (at time of study inclusion) will be included. However, patients enrolled in non-interventional, real-world study may still be eligible.	[G]
8	To reduce missing data due to lost to follow-up, patients will be required to have at least one follow-up visit with the participating study center after first-line dacomitinib treatment initiation. Patients with no follow-up visit will be excluded, unless there is a documented death in the patient records before a follow-up visit date.	[H]

Figure 2. Flow Diagram of Patient Selection



Data source

Retrospective data will be available in an unstructured form. Unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as images of physician notes, neurological scans, X-rays, or narrative fields in a database. Unstructured data will be abstracted manually by a trained research associate into a set of pre-specified data tables by filling up a case report form (CRF) and subsequently entered a study-specific electronic data capture (EDC) via a standardized eCRF interface.

For prospective patients, investigators will be provided with a point of care data collection toolkit known as the source template. A source template is the paper CRF provided to assist the investigators in collecting high quality study data while focusing on attending to the patients' clinical needs under real-world settings. A study investigator will record the required study data into the source template during a pateint's visit. An assigned and supervised research personnel (eg, a clinical research associate) will later assist the study investigator to transfer the recorded data from the source template to the eCRF. The filled source template will remain as part of the clinical document of the investigator and participating center.

Depending on the CRF design, structure and complexity, it may also be feasible for the investigator to enter the data directly into the eCRF. Programming of edit checks to identify discrepant data entered and to check for accuracy will be performed.

2.2 STUDY OBJECTIVES

The overall objective is to describe the clinical and disease characteristics, therapeutic patterns of dacomitinib use and outcomes in Asian advanced NSCLC EGFR mutation-positive populations treated with dacomitinib as a first-line treatment.

The primary objectives are:

1. To describe demographics, as well as clinical and disease characteristics of patients on first-line dacomitinib therapy for treatment of EGFR mutation-positive advanced NSCLC.

2. To describe starting dose of dacomitinib as first-line therapy, dose modification (if any), related timing and reason for dose modification, interruption or discontinuation.

3. To describe duration of dacomitinib therapy and time-to-treatment failure (TTF).

The secondary objectives are:

1. To describe real-world PFS of patients.

2. To characterize all adverse events (AEs) for patients treated with dacomitinib.

3. To describe TTF, real-world PFS, overall survival (OS) and AEs, as well as starting dose and dose modification of dacomitinib in a subgroup of patients with common EGFR mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China.

The exploratory objectives are:

1. To describe real-world OS of patients on first-line dacomitinib therapy.

2. To describe best tumor response to dacomitinib therapy.

3. To describe prevalence of T790M mutation emergence at disease progression to dacomitinib.

4. To describe subsequent treatments after permanent discontinuation of dacomitinib and the associated treatment durations.

3 HYPOTHESES AND DECISION RULES

There will be no hypothesis testing in this study. All statistical analyses performed will be descriptive and no *P*-values will be reported in this study.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Eligible patients who fulfilled all inclusion and exclusion criteria, and provided informed consent (or with IRB/IEC waiver of informed consent) will be included for analysis.

4.2 SAFETY ANALYSIS SET

The safety analysis set is the same as the full analysis set.

4.3 OTHER ANALYSIS SET

None.

4.4 SUBGROUPS

Outcomes including TTF, PFS, OS and AEs, as well as starting dose and dose modification of dacomitinib will be described for a subgroup of patients with common mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China. In addition, subgroup analysis may be conducted (only for OS, PFS and TTF) for all patients who tested positive with T790M mutation at disease progression and subsequently received any approved third-generation EGFR TKI, such as osimertinib or almonertinib.

Other subgroups of interest:

- Patients with common EGFR mutations (exon 19 deletion or exon 21 L858R substitution)
- Patients with dacomitinib starting doses of 30 mg or 45 mg once daily

5 STUDY VARIABLES

5.1 DEMOGRAPHIC AND PATIENT CHARACTERISTICS

Variables for demographic and patient characteristics are presented in Table 2. The types of variables are classified as continuous (CON), categorical (CAT), date (DATE) or time-to-event (TTE). Categorical variables include binary (dichotomous), nominal and ordinal variables.

Table 2. Demographic and Patient Characteristics

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
Age (at advanced NSCLC diagnosis)	CON	• If not directly available, age can be derived from 'Date of advanced NSCLC diagnosis' - 'Date of birth' • Unit in years	X		
Sex	CAT	• Categories include 'Male', 'Female' and 'Unknown'	X		
Ethnicity	CAT	• Categories include 'Chinese', 'Malay', 'Indian', 'Unknown' and 'Other'	X		
Country	CAT	• Categories include 'China', 'India' and 'Malaysia'	X		
Body weight	CON	• Measured at or at date nearest to advanced NSCLC diagnosis • Unit in kilograms (kg)	X		
Height	CON	• Measured at or at date nearest to advanced NSCLC diagnosis • Unit in centimetres (cm)	X		
Body mass index	CON	• Derived from 'Body weight' and 'Height' • Calculated as: $\frac{weight_{\ kg}}{height^{\ 2}_{\ m}}$ • Preferably the weight and height are measured on the same date	X		
Smoking status	CAT	• Categories include 'Current smoker', 'Former smoker',	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
		'Never smoker' and 'Unknown' • Status at or at date nearest to advanced NSCLC diagnosis			
ECOG performance status	CAT	• Describes a patient's level of functioning in terms of self-care, daily activity and physical ability • Definitions of status are based on criteria from ECOG (see Appendix 1) [2] • Categories include Grade 0 to 5, with a higher grade indicating worse level of functioning • Measured at dates of advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit	X	X	X
Charlson Comorbidity Index (CCI)	CON	• CCI will be derived by summation of weights assigned to each Charlson comorbidity (see Appendix 2) [3] • A higher CCI may be associated with higher likelihood of mortality	X		
Myocardial infarction	CAT	• Defined as history of definite or probable myocardial infarction • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Congestive heart failure	CAT	• Defined as exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
		• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1			
Chronic obstructive pulmonary disease	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Peptic ulcer disease	CAT	• Defined as any history of treatment for ulcer disease or history of ulcer bleeding • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Peripheral vascular disease	CAT	• Defined as intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm) • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Liver disease (mild) [c]	CAT	• Defined as chronic hepatitis (or cirrhosis without portal hypertension) • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Liver disease (moderate to severe) [c]	CAT	• Defined as cirrhosis with portal hypertension • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 3	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
Cerebrovascular disease	CAT	• Defined as history of a cerebrovascular accident with minor or no residua and transient ischemic attacks • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Connective tissue or rheumatic disease	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Diabetes (uncomplicated) [c]	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Diabetes (complicated) [c]	CAT	• Defined as diabetes with end-organ damage or complications • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		
Dementia	CAT	• Defined as chronic cognitive deficit • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 1	X		
Hemiplegia or paraplegia	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		
Moderate to severe chronic kidney disease	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		
Solid tumor (localized)	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
Solid tumor (metastatic)	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 6	X		
Leukemia	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		
Lymphoma	CAT	• Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 2	X		
Acquired immune deficiency syndrome	CAT	• Excludes asymptomatic infection with human immunodeficiency virus • Categories are 'Yes (present)' and 'No (absent)' • Weight in CCI: 6	X		
Date of initial NSCLC diagnosis	DATE	• Date of initial NSCLC diagnosis defined as the date in which NSCLC was first diagnosed, regardless of TNM stage • Date of initial NSCLC diagnosis is expected to be either before or at the date of advanced NSCLC diagnosis • Date format: DD-MMM-YYYY	X		
Date of advanced NSCLC diagnosis	DATE	• Advanced NSCLC defined as NSCLC with TNM stages IIIB-IV • Date format: DD-MMM-YYYY	X		
NSCLC histopathological subtype	CAT	• Categories include 'Adenocarcinoma', 'Squamous cell carcinoma', 'Large cell carcinoma' and 'Other'	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
		• Determined at the date of initial/advanced NSCLC diagnosis			
Clinical NSCLC staging	CAT	• Based on the AJCC 8th edition lung cancer staging (see Appendix 3) [1] • Stage (IA1, IA2, IA3, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, IVB) will depend on the combination of Tumor, Node and Metastasis (TNM) grades (see Appendix 4) • Determined at dates of initial and advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit	X	X	X
Presence of metastasis	CAT	• Determined at dates of initial and advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Categories are 'Yes' and 'No'	X	X	X
Location of metastasis	CAT	• Determined at dates of initial and advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Categories include 'Adrenal gland', 'Bones', 'Liver', 'CNS', 'NA' and 'Other'	X	X	X
Date of first EGFR mutation test	DATE	• Defined as the first EGFR mutation test at or after advanced NSCLC diagnosis and before initiation of first-line treatment • Date format: DD-MMM-YYYY	X		
Type of EGFR mutation (first	CAT	• Categories include 'Exon 19 deletion', 'Exon 21 L858R	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
EGFR mutation test)		substitution', 'T790 mutation' and 'Other' • Patient may have single or multiple mutations			
Date of subsequent mutation test or drug resistance profiling test	DATE	• Defined as the subsequent mutation test or drug resistance profiling test after first disease progression • Date format: DD-MMM-YYYY			X
Type of mutation or resistance mechanism (subsequent test)	CAT	• Categories include 'Exon 19 deletion', 'Exon 21 L858R substitution', 'T790 mutation', 'HER2 amplification', 'MET amplification', 'Small cell lung carcinoma transformation', 'Epithelial-mesenchymal transition', 'PIK3CA mutation', 'BRAF mutation', 'Other', 'Unknown', and 'NA' • Patient may have single or multiple mutations and/or drug resistance mechanisms			X
Type of specimen used for EGFR testing	CAT	• At each EGFR test • Categories include 'Tissue', 'Plasma' and 'Other'	X		X
Method of EGFR testing	CAT	• At each EGFR test • Categories include 'PCR sequencing', 'Next generation sequencing', 'Fluorescence in-situ hybridization', 'Immunohistochemistry' and 'Other'	X		X
Follow-up visit	DATE	• Defined as date of each scheduled visit to study site (hospital) for	X	X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
		assessment and treatment • Dates for events such as advanced NSCLC diagnosis, dacomitinib initiation, dacomitinib treatment changes and disease progression should also fall on a follow-up visit date • Date format: DD-MMM-YYYY			
Method of NSCLC assessment	CAT	• Determined at dates of initial/advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Categories include 'Clinical exam', 'X-ray or plain radiograph', 'CT-scan', 'MRI', 'PET', 'PET-CT', 'Ultrasound', 'Bone scan', 'SPECT' and Other	X	X	X
Presence of target lesions	CAT	• Based on the RECIST criteria v1.1 [4] and/or clinician's judgement • Determined at dates of initial/advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Categories are 'Yes' and 'No'	X	X	X
Evaluation of target lesions	CON	• Based on the RECIST criteria v1.1 [4] • Sum of longest diameters of all target lesions • Determined at dates of initial/advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Unit in cm	X	X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
Presence of non-target lesions	CAT	• Based on the RECIST criteria v1.1 [4] and/or clinician's judgement • Determined at dates of initial/advanced NSCLC diagnosis, dacomitinib initiation and each follow-up visit • Categories are 'Yes' and 'No'	X	X	X
Follow-up evaluation of target lesions	CAT	• Determined after first assessment based on the RECIST criteria v1.1 [4] • RECIST responses are 'Complete response (CR)', 'Partial response (PR)', 'Progressive disease (PD)', 'Stable disease (SD)' and 'Not evaluable'		X	X
Follow-up evaluation of non-target lesions	CAT	• Determined after first assessment based on the RECIST criteria v1.1 [4] • RECIST responses are 'Complete response (CR)', non-CR / non-PD, 'Progressive disease (PD)' and 'Not evaluable'		X	X
Follow-up evaluation of new lesions	CAT	• Determined after first assessment based on the RECIST criteria v1.1 [4] • RECIST responses are 'Complete response (CR)', non-CR / non-PD, 'Progressive disease (PD)' and 'Not evaluable'		X	X
RECIST overall tumor response	CAT	• Determined after first assessment based on the RECIST criteria v1.1 [4] • RECIST responses are 'Complete response (CR)', 'Partial response (PR)', 'Progressive disease (PD)', 'Stable		X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Advanced NSCLC diagnosis [a]	Dacomitinib initiation [b]	Subsequent follow-up
		disease (SD)' and 'Not evaluable'			
Tumor response based only on clinician's judgement	CAT	• Determined after first assessment and based only on clinician's judgement • Categories are 'Complete response (CR)', 'Partial response (PR)', 'Progressive disease (PD)', 'Stable disease (SD)' and 'Not evaluable'		X	X
Duration from advanced NSCLC diagnosis to dacomitinib initiation	CON	• Derived from 'Dacomitinib initiation date' - 'Date of advanced NSCLC diagnosis' • Unit in months	X	X	
Duration from EGFR status confirmation (first test) to dacomitinib initiation	CON	• Derived from 'Dacomitinib initiation date' - 'Date of first EGFR mutation test' • Unit in months	X	X	

Abbreviations: AJCC, American Joint Committee on Cancer; CAT, categorical; CCI, Charlson Comorbidity Index; CNS, central nervous system; CON, continuous; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TNM, Tumor Node and Metastasis.
[a] At date of advanced NSCLC diagnosis, unless otherwise specified.
[b] First-line therapy for advanced NSCLC.
[c] With mutually exclusive categories.

5.2 TREATMENT

Dacomitinib treatment and related variables are presented in Table 3.

Table 3. Treatment Variables

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
Dacomitinib (first-line) initiation date	DATE	• Defined as the first-line therapy initiated for advanced NSCLC	X		

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
		• Date format: DD-MMM-YYYY			
Dacomitinib starting oral dose	CAT	• Categories are '45 mg', '30 mg', '15 mg' and 'Other'	X		
Dacomitinib starting oral dose frequency	CAT	• Categories are 'Once daily', 'Once every two days' and 'Other'	X		
Concomitant chemotherapy and/or local treatment	CAT	• Defined as any SACT (e.g. platinum-based chemotherapy) and/or localized treatment (e.g. surgery, radiotherapy) while on first-line dacomitinib therapy • Categories are 'Yes' and 'No' • Determined at dates of dacomitinib initiation and permanent discontinuation	X	X	
First dacomitinib dose modification date	DATE	• Defined as first dacomitinib dose modification (any dose change) of initial dacomitinib therapy • Date format: DD-MMM-YYYY		X	
Dacomitinib oral dose (first modification)	CAT	• Categories are '45 mg', '30 mg', '15 mg' and 'Other'		X	
Dacomitinib oral dose frequency (first modification)	CAT	• Categories are 'Once daily', 'Once every two days' and 'Other'		X	
Second dacomitinib dose modification date	DATE	• Defined as the second dacomitinib dose modification of previous dacomitinib therapy • Date format: DD-MMM-YYYY		X	
Dacomitinib oral dose (second modification)	CAT	• Categories are '45 mg', '30 mg', '15 mg' and 'Other'		X	

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
Dacomitinib oral dose frequency (second modification)	CAT	• Categories are 'Once daily', 'Once every two days' and 'Other'		X	
First dacomitinib dose interruption start date	DATE	• Defined as the first time for dacomitinib treatment being temporarily stopped • Date format: DD-MMM-YYYY		X	
First dacomitinib dose interruption end date	DATE	• Defined as the first time for dacomitinib treatment being restarted (after first interruption) • Date format: DD-MMM-YYYY		X	
Reason for dacomitinib dose modification / interruption	CAT	• Defined as any clinical or adverse event related to dacomitinib dose modification or interruption • Categories include common adverse reactions occurring in patients who received dacomitinib in ARCHER 1050 trial[5] • Determined at first and second dacomitinib dose modification, as well as first and second dacomitinib dose interruption		X	X
Duration of first dose interruption	CON	• Derived from 'First dacomitinib dose interruption end date' - 'First dacomitinib dose interruption start date' + 1 day • Unit in months		X	
Second dacomitinib dose interruption start date	DATE	• Defined as the second time for dacomitinib treatment being temporarily stopped • Date format: DD-MMM-YYYY		X	

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
Second dacomitinib dose interruption end date	DATE	• Defined as the second time for dacomitinib treatment being restarted (after second interruption) • Date format: DD-MMM-YYYY		X	
Duration of second dose interruption	CON	• Derived from 'Second dacomitinib dose interruption end date' - 'Second dacomitinib dose interruption start date' + 1 day • Unit in months		X	
Initiation of new treatment during dose interruption	CAT	• Determined between respective start and end dates of the first and second dose interruptions • Categories are 'Yes' and 'No'		X	
Dacomitinib permanent discontinuation date	DATE	• Defined as date in which dacomitinib was permanently discontinued i.e. no further treatment until end of follow-up • Date format: DD-MMM-YYYY		X	
Duration of first-line dacomitinib treatment	CON	• Derived from 'Dacomitinib permanent discontinuation date' - 'Dacomitinib initiation date' + 1 day • Unit in months • Alternatively, as described below, duration will be derived from 'Dacomtinib last dose date' - 'Dacomitinib initiation date' + 1 day • The last visit date before end of study will be considered as last dose date for patients who are still on first-line dacomitinib at end of		X	

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
		follow-up. For interim analysis, the last visit date before data cut-off will be considered as last dose date for patients who are still on first-line treatment at time of interim analysis. • For patients who died (while on first-line dacomitinib), the date of death will be considered as last dose date • For patients lost to follow-up (while on first-line dacomitinib), the last visit date before lost to follow-up will be considered as last dose date • For patients who withdrew consent (while on first-line dacomitinib), the last visit date before consent withdrawal will be considered as last dose date • No censoring			
Subsequent treatment initiation date	DATE	• Defined as initiation date for subsequent treatment after permanent discontinuation of first-line dacomitinib • For example, the second-line therapy will be the second treatment (apart from dacomitinib) received by patient for treatment of advanced NSCLC • Determined for the second-line, third-line and fourth-line treatment, if any • Date format: DD-MMM-YYYY		X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
Subsequent treatment	CAT	• Name of subsequent treatment after permanent discontinuation of first-line dacomitinib • Categories include 'Gefitinib', 'Erlotinib', 'Afatinib', 'Osimertinib', 'Almonertinib', 'Olmutinib', 'Bevacizumab', 'Ramucirumab', 'Pembrolizumab', 'Nivolumab', 'Chemotherapy', 'Radiotherapy', 'Surgery', 'No active treatment' and 'Other' • Determined for the second-line, third-line and fourth-line treatment, if any		X	X
Subsequent treatment permanent discontinuation date	DATE	• Defined as discontinuation date for subsequent treatment • Determined for the second-line, third-line and fourth-line treatment, if any • Date format: DD-MMM-YYYY		X	X
Reason for dacomitinib permanent discontinuation	CAT	• Defined as any clinical or adverse event related to dacomitinib permanent discontinuation • Categories include 'Lack of response', 'Disease progression', 'Patient preference', 'Medication cost', and common adverse reactions occurring in patients who received dacomitinib in ARCHER 1050 trial[5]		X	X
Duration from dacomitinib discontinuation to	CON	• Derived from 'Second-line initiation date' -		X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
second-line treatment		'Dacomitinib permanent discontinuation date' • Unit in months			
Duration from dacomitinib discontinuation to third-line treatment	CON	• Derived from 'Third-line initiation date' - 'Dacomitinib permanent discontinuation date' • Unit in months		X	X
Duration from dacomitinib discontinuation to fourth-line treatment	CON	• Derived from 'Fourth-line initiation date' - 'Dacomitinib permanent discontinuation date' • Unit in months		X	X
Duration of second-line treatment	CON	• Derived from 'Second-line discontinuation date - 'Second-line initiation date' + 1 day • Unit in months • Alternatively, as described below, duration will be derived from 'Second-line last dose date' - 'Second-line initiation date' + 1 day • The last visit date before end of study will be considered as last dose date for patients who are still on second-line treatment at end of follow-up. For interim analysis, the last visit date before data cut-off will be considered as last dose date for patients who are still on second-line treatment at time of interim analysis. • For patients who died (while on second-line treatment), the date of death will be considered as last dose date • For patients lost to follow-up (while on second-line treatment), the last visit date before		X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
		lost to follow-up will be considered as last dose date • For patients who withdrew consent (while on second-line dacomitinib), the last visit date before consent withdrawal will be considered as last dose date • No censoring			
Duration of third-line treatment	CON	• Derived from 'Third-line discontinuation date' - 'Third-line initiation date' + 1 day • Unit in months • Alternatively, as described below, duration will be derived from 'Third-line last dose date' - 'Third-line initiation date' + 1 day • The last visit date before end of study will be considered as last dose date for patients who are still on third-line treatment at end of follow-up. For interim analysis, the data cut-off date will be considered as last dose date for patients who are still on third-line treatment at time of interim analysis. • For patients who died (while on third-line treatment), the date of death will be considered as last dose date • For patients lost to follow-up (while on third-line treatment), the last visit date before lost to follow-up will be considered as last dose date		X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Treatment changes [b]	End of follow-up
		• For patients who withdrew consent (while on third-line dacomitinib), the last visit date before consent withdrawal will be considered as last dose date • No censoring			
Dacomitinib last oral dose	CAT	• Defined as last oral dose of dacomitinib prior to permanent discontinuation • Categories are '45 mg', '30 mg', '15 mg' and 'Other'		X	
Dacomitinib last oral dose frequency	CAT	• Defined as last oral frequency of dacomitinib prior to permanent discontinuation • Categories are 'Once daily', 'Once every two days' and 'Other'		X	
Number of dacomitinib dose modifications	CAT	• Categories are 'None', 'One', 'Two' and 'More than two' • Information on only the first two dose modifications will be collected			X
Number of dacomitinib dose interruptions	CAT	• Categories are 'None', 'One', 'Two' and 'More than two' • Information on only the first two dose interruptions will be collected			X
Number of subsequent lines of therapy after dacomitinib permanent discontinuation	CAT	• Categories are 'None', 'One', 'Two' and 'More than two' • Information on subsequent three lines of therapies (second-line, third-line and fourth-line) will be collected			X

Abbreviations: NSCLC, non-small cell lung cancer; SACT, systemic anti-cancer therapy.
[a] First-line therapy for advanced NSCLC.
[b] Consist of dacomitinib dose modification, interruption and permanent discontinuation. Treatment changes will be captured during follow-up visits after dacomitinib initiation.

5.3 OUTCOMES

5.3.1 Definition of study outcomes

Study outcomes and related variables are presented in Table 4.

Table 4. Study Outcomes

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Disease first progression [b]	Subsequent follow-up
Study end date	DATE	• Defined as date of death, lost to follow-up, withdrawal of consent or end of study, whichever comes first • Date format: DD-MMM-YYYY	X	X	X
Status at end of study	CAT	• Categories include 'Death', 'Withdrawal of consent', 'Alive until end of study follow-up', 'Loss to follow-up' and 'Unknown' • Patients who withdrew consent or with unknown status may be considered as loss to follow-up	X	X	X
Date of death	DATE	• Defined as date of death from any cause • Date format: DD-MMM-YYYY	X	X	X
Real-world OS	CON; TTE	• Measured in months from date of dacomitinib initiation, to date of death from any cause • Patients who remained alive (i.e. no date of death) until end of follow-up will be censored at the date of	X	X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Disease first progression [b]	Subsequent follow-up
		last known contact/visit date • Patients lost to follow-up will be censored based on the last known contact/visit date			
Date of first disease progression	DATE	• Date of progression will be the earliest documented date of cancer worsening based on radiologist's interpretation of the imaging and/or clinician's assessment, and after initiation of first-line dacomitinib treatment • Date format: DD-MMM-YYYY		X	
Date of subsequent disease progression	DATE	• Date of the second (or third progression) will be documented after initiation of the second-line (or third-line) treatment • Date format: DD-MMM-YYYY			X
Real-world PFS	CON; TTE	• Measured in months from date of dacomitinib initiation to date of first disease progression or death from any cause, whichever comes first • Patients without disease progression and remained alive (i.e. no date of death) until end of follow-up will be censored at the date of last known contact/visit date • Patients lost to follow-up will be censored based on the last known contact/visit date	X	X	X

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Disease first progression [b]	Subsequent follow-up
T790M mutation status	CAT	• Defined as whether a T790M mutation is detected at the time of first disease progression among those who were tested • Derived from 'Type of mutation or resistance mechanism (subsequent test)' • Categories are 'Yes' and 'No'		X	
Time-to-treatment failure (TTF) for dacomitinib	CON; TTE	• Measured in months from date of dacomitinib initiation to date of dacomitinib permanent discontinuation (for any reason), first disease progression, or death (from any cause), whichever comes first • Patients who remained on dacomitinib without an event until end of follow-up will be censored at the date of last known contact/visit date • Patients lost to follow-up will be censored based on the last known contact/visit date		X	X
Best tumor response to dacomitinib	CAT	• Defined as the best response recorded (based on the RECIST and/or clinician's judgement) from date of dacomitinib initiation to date of first disease progression, dacomitinib permanent discontinuation date, or end of study whichever comes first		X	

Variable	Type	Operational definition / description	Data collection timepoints		
			Dacomitinib initiation [a]	Disease first progression [b]	Subsequent follow-up
		• Categories for overall tumor response are 'Complete response (CR)', 'Partial response (PR)', 'Progressive disease (PD)', 'Stable disease (SD)' and 'Not evaluable'			
Occurrence of adverse event	CAT	• Categories are 'Yes' and 'No'	X	X	X
Type of adverse event	CAT	• Defined as any adverse event which may or may not be related to use of dacomitinib • Event is captured as free-text and will be subsequently mapped to MedDRA standard terms.	X	X	X
Relationship of adverse event to dacomitinib	CAT	• Categories are 'Related' and 'Not related'	X	X	X
Severity of adverse event	CAT	• Categories are 'Severe' and 'Non-severe'	X	X	X
Adverse event start date	DATE	• Defined as adverse event start date • Date format: DD-MMM-YYYY	X	X	X
Adverse event end date	DATE	• Defined as adverse event start date • Date format: DD-MMM-YYYY	X	X	X

Abbreviations: OS, overall survival; CR, complete response; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TTE, time-to-event; TTF; time-to-treatment failure.

[a] First-line therapy for advanced NSCLC.

[b] Disease progression after diagnosis of advanced NSCLC and use of dacomitinib as first-line treatment.

5.3.2 Derivation rule for time-to-event outcomes

Based on the actual data that has been collected, the following event and censoring senarios are further specified for time-to-event outcomes including OS, PFS, and TTF.

Outcome	Event	Censoring
OS	For a patient with event (i.e., death), the following logic should be followed to find the date of event: 1. Find death date for those who died.	For a patient who died but death date is partially or completely missing: 1. Censor the patient at the last available complete date among the relevant variables[1] and change the censoring reason to "Lost to follow-up". For the remaining patients with NO death identified: 2. If status = "Alive until end of study follow-up" then censoring reason is "Alive at the end of study". • If last known to be alive date is partially or completely missing, then the last available complete date will be used for censoring[1] 3. If status = "Lost to follow-up" then censoring reason is "Lost to follow-up". • If lost to follow-up date is partially or completely missing, then the last available complete date will be used for censoring[1] 4. If status = "Withdrawal of consent" then censoring reason is "Withdrew consent". • If withdrawal date is partially or completely missing, then the last available complete date will be used for censoring[1] 5. If status = "Unknown", re-classify status to "Lost to follow-up". Follow the logic described in step 2 to find date for censoring.
PFS	For a patient with event (i.e., death or first progression), the following logic should be followed to find the date of event: 1. Find death date for those who died. Find first disease progression date for those who have disease progression. If both dates present, choose earlier date (i.e. first disease progression date). If only one date present, choose that date. 2. Compare the event date with second-line therapy initiation date: • If event occurs at or before second-line therapy, use the event date. • If event occurs after second-line therapy, censor this patient (refer to censoring #1). • If the second-line therapy initiation date is missing, use event date.	For patients with event but event date falls into following scenarios, censor accordingly and change the censoring reason to "Start of new anti-cancer therapy": 1. If second-line treatment is started and the event occurs after initiation of second-line treatment, censor using the last assessment date prior to start of second-line treatment. 2. If event date is missing and second-line treatment is started for this patient, censor using the last assessment date prior to the start of second-line therapy 3. If last assessment date is before dacomitinib initiation date, censor this patient at dacomitinib initiation date. For the remaining patients with NO event identified, we will use the last assessment date as censoring date. If it is missing, the last available complete date will be used for censoring[2] 4. If status = "Alive until end of study follow-up" then censoring reason is "Alive with no progression at the end of study". 5. If status = "Lost to follow-up" then censoring reason is "Lost to follow-up". 6. If status = "Withdrawal of consent" then censoring reason is "Withdrew consent". 7. If status = "Unknown", re-classify status to "Lost to follow-up".
TTF	For a patient with event (i.e., permanent discontinuation, first disease progression	For patients with event but event date falls into following scenarios, censor accordingly and change the censoring reason to "Start of new anti-cancer therapy":

	or death), the following logic should be followed to find the date of event: 1. Find dacomitinib permanent discontinuation date for those who discontinued dacomitinib. Find first disease progression date for those who have disease progression. Find death date for those who died. If two or three dates present for one subject, choose the earliest date. If only one date present, choose that date. 2. Compare the event date with second-line therapy initiation date: • If event occurs at or before second-line therapy, use the event date. • If event occurs after second-line therapy, censor this patient (refer to censoring #1). • If the second-line therapy initiation date is missing, use event date.	1. If second-line treatment is started and the event occurs after initiation of second-line treatment, censor using the last assessment date prior to start of second-line treatment. 2. If event date is missing and second-line treatment is started for this patient, censor using the last assessment date prior to the start of second-line therapy 3. If last assessment date is before dacomitinib initiation date, censor this patient at dacomitinib initiation date. For the remaining patients with NO event identified, we will use the last assessment date as censoring date. If it is missing, the last available complete date will be used for censoring[2] 4. If status = "Alive until end of study follow-up" then censoring reason is "Alive with no progression at the end of study". 5. If status = "Lost to follow-up" then censoring reason is "Lost to follow-up". 6. If status = "Withdrawal of consent" then censoring reason is "Withdrew consent". 7. If status = "Unknown", re-classify status to "Lost to follow-up".
Note: [1] Choose the last (or latest) available date among the relevant date variables: date of last known contact (LSTKNWDT), date last known to be alive (LASTKNDT), lost to follow-up date (FOLLOWDT) and last visit date (LAST_VST_DT). [2] Choose the last (or latest) available date among the relevant date variables: date of last known contact (LSTKNWDT), date last known to be alive (LASTKNDT), lost to follow-up date (FOLLOWDT) and last visit date (LAST_VST_DT).		

6 HANDLING OF MISSING VALUES

In primary analysis, the number of patients with missing data for each variable will be reported. No imputation is planned to address missing data in this study. However, sensitivity analysis will be conducted for best tumor response to dacomitinib among patients with best response available.

Based on eCRF design, 'Unknown' and 'Missing' categories for variables will be reported if applicable. For variables without 'Unknown' category, they will be treated as missing data if there is no valid data input.

In addition, as part of sensitivity analysis, the following imputation methods will be applied for partially missing date for permanent discontinuation date of dacomitinib, disease assessment date, death date,and first progression date in the calculation of time-to-event outcomes, including OS, PFS, and TTF.

- If only the day in the event date is missing, the missing day will be imputed as the 1st day of the month.
- No imputation will be performed if there is missing year or/and month.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Means, standard deviations (STDs), medians and interquartile ranges (IQRs), minimums and maximums will be provided for continuous variables when performing descriptive analysis of continuous data. Frequencies (counts) and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Time-to-event data such as real-world OS, PFS and TTF will be analysed using the Kaplan Meier method, with 2-sided 95% confidence intervals (CIs) estimating median time to event. The CIs for the median will be calculated according to Brookmeyer and Crowley, 1982. Time duration may be presented as days, weeks or months, depending on data.

Results will be presented as total, as well as for each country. For findings to be meaningful, analyses will only be performed if there are at least 20 patients in each cell of a summary table.

Table 5. Statistical Output

Global rule	Description
Decimal places	• Minimum, Maximum – 2 decimal places • Mean, SD, Median, Q1, Q3 – 2 decimal places
Percentages	• Based on the total number of patients in the analysis set unless otherwise specified.
Lack of observations	• If there is no observation, summary statistics will be displayed as "-"

7.2 STATISTICAL ANALYSES

Please refer to Table 6 (Section 6.2.6) for further information on each variable. All analyses will be conducted on the Full Analysis Set, and results presented for all patients (total) and by dacomitinib starting dose level. Patients who were enrolled but violated inclusion/exclusion criteria will be listed.

7.2.1 Analyses related to primary objectives

Primary objective #1: To describe demographics, as well as clinical and disease characteristics of patients on first-line dacomitinib therapy for treatment of EGFR mutation-positive advanced NSCLC.

All enrolled patients should have EGFR mutation-positive advanced NSCLC. Descriptive statistics will be presented on their demographics, as well as clinical and disease characteristics. Baseline characteristics are based on the last non-missing measurement collected prior to dacomitinib initiation.

The following baseline demographics will be assessed:

- Age
- Sex

- Ethnicity
- Body mass index (derived from body weight and height)
- Smoking status
- Charlson Comorbidity Index (derived from comorbidities)
- Comorbidities based on the Charlson Comorbidity Index

The following clinical and disease characteristics may be assessed at multiple timepoints including at diagnosis of advanced NSCLC and initiation of dacomitinib:

- NSCLC histopathological subtype
- Clinical NSCLC staging
- Presence of metastasis
- Location of metastasis
- ECOG performance status
- Method of NSCLC assessment
- First EGFR mutation test
  - Type of EGFR mutation
  - Type of specimen
  - Method of testing
- Duration from advanced NSCLC diagnosis to dacomitinib initiation
- Duration from EGFR status confirmation (first test) to dacomitinib initiation

Primary objective #2: To describe starting dose of dacomitinib as first-line therapy, dose modification (if any), related timing and reason for dose modification, interruption or discontinuation.

Descriptive statistics will be presented on dacomitinib treatment regimen, treatment changes (dose modification, dose interruption and permanent discontinuation) and concomitant therapies prescribed at dacomitinib initiation and at permanent discontinuation of dacomitinib. Some analyses related to dacomitinib discontinuation will be covered under 'Primary objective #3'.

The following treatment variables will be described for dacomitinib initiation:

- Dacomitinib starting oral dose

- Dacomitinib starting oral dose frequency
- Concomitant chemotherapy and/or local treatment (including surgery and radiotherapy) at dacomitinib initiation

The following treatment changes related to dacomitinib dose modification will be described:

- Dacomitinib oral dose (first modification)
- Dacomitinib oral dose frequency (first modification)
- Dacomitinib oral dose (second modification)
- Dacomitinib oral dose frequency (second modification)
- Reason for dacomitinib dose modification (first and second)
- Number of dacomitinib dose modifications

The following treatment changes related to dacomitinib dose interruption will be described:

- Duration of first dose interruption
- Duration of second dose interruption
- Reason for dacomitinib dose interruption (first and second)
- Number of dacomitinib dose interruptions

The following treatment changes related to dacomitinib permanent discontinuation will be described:

- Dacomitinib last oral dose
- Dacomitinib last oral dose frequency
- Reason for dacomitinib permanent discontinuation
- Concomitant chemotherapy and/or local treatment at dacomitinib discontinuation

The following will be assessed for duration of first-line dacomitinib treatment by starting dose and dose modification status:

- Duration on the initial starting dose
- Duration on the first modified dose
- Duration on the second modified dose

Primary objective #3: To describe duration of dacomitinib therapy and time-to-treatment failure (TTF).

Descriptive statistics will be presented for duration of first-line dacomitinib treatment, while time-to-treatment failure (TTF) will be analysed as time-to-event outcome. Median and 95% CI for TTF will be presented, with its Kaplan-Meier curve.

Calculation of duration of first-line dacomitinib treatment is measured in months from date of initiation to date of dacomitinib discontinuation (or last dose). The last visit date before data cut-off will be considered as last dose date for patients who are still on dacomitnib at time of interim analysis. The last visit date before study end date will be considered as last dose date for patients who are still on dacomitinib at end of follow-up. For patients who died (while on dacomitinib), the date of death will be considered as last dose date. For patients lost to follow-up, the last visit date before lost to follow-up will be considered as last dose date.

Calculation of TTF is measured in months from date of first-line dacomitinib treatment to date of dacomitinib permanent discontinuation, first disease progression or death, whichever occurs first. Patients who remained on dacomitinib without an event until end of follow-up or are lost to follow-up will be censored based on the last known contact/visit date.

The following will be assessed for dacomitinib permanent discontinuation

- Duration of first-line dacomitinib treatment:
    - Duration of first-line dacomitinib (any starting doses until permanent discontinuation)
- TTF for dacomitinib

7.2.2 Analyses related to secondary objectives

Secondary objective #1: To describe real-world progression-free survival (PFS) of patients.

Calculation of PFS is measured in months from date of first-line dacomitinib treatment to date of first disease progression or death from any cause, whichever comes first. Patients without disease progression and remained alive, or are lost to follow-up will be censored based on last known contact/visit date.

These will be analysed as time-to-event outcomes with Kaplan-Meier curves. Median PFS and their respective 95% CI will be presented.

The following outcome will be assessed:

- Real-world PFS from dacomitinib initiation

Secondary objective #2: To characterize all adverse events (AEs) for patients treated with dacomitinib.

The FDA has generally defined an AE as any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product (i.e. dacomitinib) and which does not necessarily have

to have a causal relationship with this product. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary.

The following will be assessed for all-causality and treatment-related AEs or SAEs:

- Patients with AEs
- Action taken for AEs
- AE by system organ class (SOC) and preferred term (PT)
- Patients with SAEs
- SAE by PT

The AE and SAE tables will be stratified by dacomitinib starting dose.

Secondary objective #3: To describe TTF, PFS, overall survival (OS) and AEs, as well as starting dose and dose modification of dacomitinib in a subgroup of patients with common EGFR mutations (exon 19 deletion or exon 21 L858R substitution) enrolled in China.

The following objectives will be repeated for a subgroup of patients with common EGFR mutations enrolled in China:

- Primary objectives #1-3
- Secondary objectives #1 and #2
- Exploratory objectives #1 and #2

7.2.3 Analyses related to exploratory objectives

Exploratory objective #1: To describe real-world OS on first-line dacomitinib therapy.

Real-world OS will be analysed as time-to-event outcome with Kaplan-Meier curve. Median OS and its respective 95% CI will be presented.

OS is measured in months from date of dacomitinib initiation to date of death from any cause. Patients who remained alive (i.e. no date of death) until end of follow-up, or are lost to follow-up will be censored based on the last known contact/visit date.

The following outcome will be assessed:

- Real-world OS from dacomitinib initiation

Exploratory object #2: To describe best tumor response to dacomitinib therapy.

Descriptive statistics will be presented for the overall best tumor response (based on either RECIST or clinician's judgement) from dacomitinib initiation to first disease progression, dacomitinib permanent discontinuation or end of study, whichever comes first.
The following variables will be described:

- Assessment of best tumor response (using RECIST criteria or clinician's judgement)
- Best tumor response to dacomitinib

In addition, sensitivity analysis will be conducted for best tumor response to dacomitinib among patients with no missing values.

Exploratory objective #3: To describe prevalence of T790M mutation emergence at disease progression to dacomitinib.

Descriptive statistics will be presented for T790M mutation and other mutations or drug resistance mechanisms detected at first disease progression.

The following will be assessed after first disease progression:

- Subsequent EGFR mutation or drug resistance profiling test
  - Type of EGFR mutation or drug resistance mechanism
  - T790M mutation
  - Type of specimen
  - Method of testing

Exploratory objective #4: To describe subsequent treatments after permanent discontinuation of dacomitinib and the associated treatment durations.

After permanent discontinuation of first-line dacomitinib treatment, patients may be initiated on other therapies. Descriptive statistics will be presented for subsequent therapies prescribed up to the fourth-line treatment.

The following will be described:

- Subsequent treatment (second-, third- and fourth-line)
- Duration from dacomitinib discontinuation to second-line treatment
- Duration of second-line treatment
- Duration from dacomitinib discontinuation to third-line treatment
- Duration of third-line treatment

- Duration from dacomitinib discontinuation to fourth-line treatment
- Number of subsequent lines of therapy after dacomitinib permanent discontinuation

7.2.4 Other analyses

If data permits (depending on sample size), below stratified or subgroup analyses may be conducted.

- By country (China, India or Malaysia);
- By starting dose and frequency of dacomitinib;
  - 30 mg once daily
  - 45 mg once daily
  - Other doses
- By common EGFR mutations at baseline;
  - Exon 19 deletion
  - Exon 21 L858R substitution
- Patients who started with dacomitinib, tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI, such as osimertinib or almonertinib

Subgroup analysis for retrospective and mixed/prospective patients may be conducted if the data quality and completeness varies significantly between the patient groups. Otherwise, all patients (regardless of data collection approach) will be included for analyses.

7.2.5 Interim analysis

Interim analysis will be conducted four months after enrolment end date to fulfil regulatory requirement. All objectives, except for overall survival, will included for interim analysis.

7.2.6 Summary of analyses

Statistical analyses on demographic and patient characteristics, treatment patterns and outcomes are summarized in Table 6.

Table 6. Planned Statistical Analyses

Variable	Protocol objective number	Analysis set (population)	Statistical analysis	Strata or subgroup
Age (at advanced NSCLC diagnosis)	Primary #1	All enrolled patients	• Mean and standard deviation (STD); Median and interquartile range (IQR) • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Sex	Primary #1	All enrolled patients	• Count and percentage	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China

				• Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Ethnicity	Primary #1	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Body mass index	Primary #1	All enrolled patients	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease

				progression and subsequently received any approved third generation EGFR TKI
Smoking status	Primary #1	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Charlson Comorbidity Index	Primary #1	All enrolled patients	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any

				approved third generation EGFR TKI
Comorbidities	Primary #1	All enrolled patients	• Count and percentage for presence of each comorbidity	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
NSCLC histopathological subtype	Primary #1	All enrolled patients	• Counts and percentages for NSCLC histologic subtypes	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI

Clinical NSCLC staging	Primary #1	All enrolled patients	• Counts and percentages for TNM stages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Presence of metastasis	Primary #1	All enrolled patients	• Count and percentage for presence of metastasis	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Location of metastasis	Primary #1	Enrolled patients with metastasis	• Counts and percentages for sites of metastasis	• By country

				• By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
ECOG performance status	Primary #1	All enrolled patients	• Counts and percentages for ECOG Grades	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Method of initial NSCLC assessment	Primary #1	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations

				• By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Type of EGFR mutation (first EGFR mutation test)	Primary #1	All enrolled patients	• Counts and percentages of EGFR mutation subtypes at baseline	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Type of specimen used for EGFR testing (first test)	Primary #1	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose

				• Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Method of EGFR testing (first test)	Primary #1	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
DurationDuration from advanced NSCLC diagnosis to dacomitinib initiation	Primary #1	All enrolled patients	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China

				• Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
DurationDuration from EGFR status confirmation (first test) to dacomitinib initiation	Primary #1	All enrolled patients	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Dacomitinib starting oral dose	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib starting oral dose frequency	Primary #2	All enrolled patients	• Counts and percentages	• By country

				• By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib oral dose (first modification)	Primary #2	Enrolled patients with first dose modification	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib oral dose frequency (first modification)	Primary #2	Enrolled patients with first dose modification	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib oral dose (second modification)	Primary #2	Enrolled patients with second dose modification	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China

Dacomitinib oral dose frequency (second modification)	Primary #2	Enrolled patients with second dose modification	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Number of dacomitinib dose modifications	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Duration of first dose interruption	Primary #2	Enrolled patients with first dose interruption	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Duration of second dose interruption	Primary #2	Enrolled patients with second dose interruption	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China

Number of dacomitinib dose interruptions	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib last oral dose	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Dacomitinib last oral dose frequency	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Reason for dacomitinib dose modification / interruption	Primary #2	Enrolled patients with dose modification / interruption	• Counts and percentages of adverse events • Counts and percentages of the reasons for dose modification (first and second) • Counts and percentages of the reasons for dose interruption (first and second)	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China

Reason for dacomitinib permanent discontinuation	Primary #2	Enrolled patients who discontinued dacomitinib	• Counts and percentages of adverse events • Counts and percentages of the reasons for permanent discontinuation	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Concomitant chemotherapy and/or local treatment	Primary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Duration of first-line dacomitinib treatment	Primary #3	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Time-to-treatment failure (TTF) for dacomitinib	Primary #3	All enrolled patients	• Kaplan-Meier curve	• By country

			• Median and 95% CI for median TTF • Counts and percentages of patients who remained on dacomitinib at specific timepoints (6, 12, 18 and 24 months) after dacomitinib initiation	• By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Real-world PFS	Secondary #1	All enrolled patients	• Kaplan-Meier curve • Median and 95% CI for median PFS • Counts and percentages of patients who were progression-free at specific timepoints (6, 12, 18 and 24 months) after dacomitinib initiation	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Adverse event	Secondary #2	All enrolled patients	• Counts and percentages of adverse events • Counts and percentages of serious adverse events	• By country • By common EGFR mutations

			• Counts and percentages of adverse events related to dacomitinib	• By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Outcome after adverse event	Secondary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Action taken for dacomitinib (after adverse event)	Secondary #2	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China
Real-world OS	Exploratory #1	All enrolled patients	• Kaplan-Meier curve • Median, 95% CI for median OS • Counts and percentages of patients who survived at specific timepoints (6, 12, 18 and 24 months) • Starting from (i) dacomitinib initiation, and (ii) advanced NSCLC diagnosis	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any

				approved third generation EGFR TKI
Assessment of best tumor response	Exploratory #2	All enrolled patients	• Counts and percentages of assessment performed using RECIST criteria or clinician's judgement	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI
Best tumor response to dacomitinib	Exploratory #2	Enrolled patients with assessment of tumor response	• Counts and percentages of best tumor responses to dacomitinib	• By country • By common EGFR mutations • By dacomitinib starting dose • Subgroup with common EGFR mutations in China • Subgroup who tested positive with T790M mutation at disease progression and subsequently received any approved third generation EGFR TKI

Type of mutation or resistance mechanism (subsequent test)	Exploratory #3	Enrolled patients with disease progression	• Count and percentage of patients tested for mutation or drug resistance profile at disease progression • Counts and percentages of EGFR mutation subtypes or resistance mechanisms at disease progression	• By country • By common EGFR mutations • By dacomitinib starting dose
Type of specimen used for EGFR testing (subsequent test)	Exploratory #3	Enrolled patients with disease progression	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose
Method of EGFR testing (subsequent test)	Exploratory #3	Enrolled patients with disease progression	• Counts and percentages	• By country • By common EGFR mutations • By dacomitinib starting dose
T790M mutation	Exploratory #3	Enrolled patients with disease progression	• Count and percentage of patients with acquired T790M mutation post-disease progression among those tested	• By country • By common EGFR mutations • By dacomitinib starting dose
Subsequent treatment	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Count and percentage of patients who discontinued dacomitinib • Counts and percentages of treatments (second-, third- and fourth-line)	• By country • By common EGFR mutations • By dacomitinib starting dose
DurationDuration from dacomitinib	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country

discontinuation to second-line treatment				• By common EGFR mutations • By dacomitinib starting dose
Duration of second-line treatment	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose
DurationDuration from dacomitinib discontinuation to third-line treatment	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose
Duration of third-line treatment	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose
DurationDuration from dacomitinib discontinuation to fourth-line treatment	Exploratory #4	Enrolled patients who discontinued dacomitinib	• Mean and STD; Median and IQR • Minimum and maximum	• By country • By common EGFR mutations • By dacomitinib starting dose
Number of subsequent lines of therapy after dacomitinib permanent discontinuation	Exploratory #4	All enrolled patients	• Counts and percentages	• By country • By common EGFR mutations

				• By dacomitinib starting dose

8 REFERENCES

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2. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
3. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
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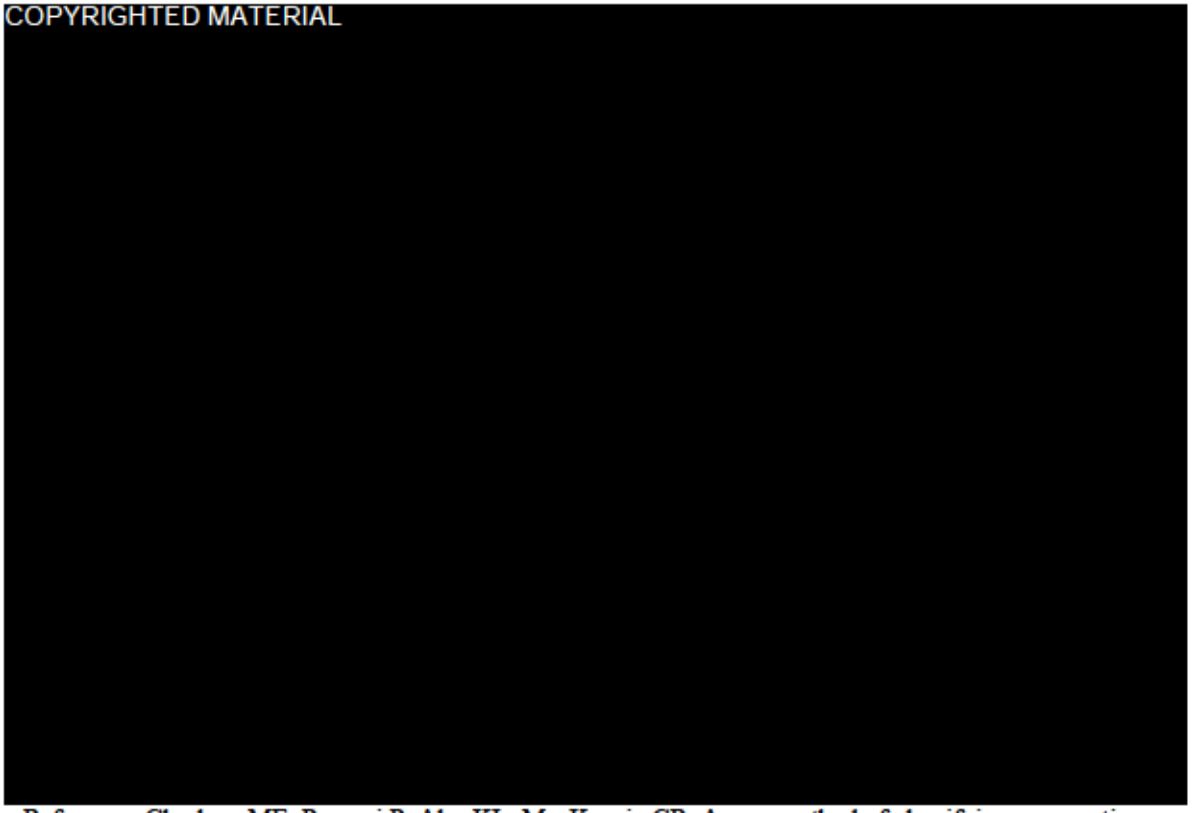
9 APPENDICES

9.1 APPENDIX 1: DESCRIPTION OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
Grade 0	Fully active, able to carry on all pre-disease performance without restriction.
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
Grade 2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
Grade 3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
Grade 5	Dead

Reference: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

9.2 APPENDIX 2: LIST OF CONDITIONS IN THE CHARLSON COMORBIDITY INDEX



Reference: Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40(5):373-383.
[a] With mutually exclusive categories.

9.3 APPENDIX 3: LUNG CANCER STAGE GROUPING BASED ON TUMOR, NODE AND METASTASIS (TNM) GRADES

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.

9.4 APPENDIX 4: DEFINITIONS FOR TUMOR, NODE AND METASTASIS (TNM) DESCRIPTORS

Grade	T (primary tumor)
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤3 cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways
T1a	Tumor ≤1cm
T1b	Tumor >1 but ≤2cm
T1c	Tumor >2 but ≤3cm
T2	Tumor >3 but ≤5cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum
T2a	Tumor >3 but ≤4cm
T2b	Tumor >4 but ≤5cm
T3	Tumor >5 but ≤7cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor >7cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
	N (regional lymph nodes)
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
	M (distant metastasis)
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases (1 or >1 organ)

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.