CLINICAL STUDY PROTOCOL

A MULTICENTER, OPEN-LABEL PHASE 1 STUDY OF DS-1205c IN COMBINATION WITH GEFITINIB IN SUBJECTS WITH METASTATIC OR UNRESECTABLE EGFR-MUTANT NON-SMALL CELL LUNG CANCER

DS1205-A-J102

VERSION 5.0, 29 JULY 2019

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VERSION 3.0, 29 OCTOBER 2018

VERSION 2.0, 29 JUNE 2018

VERSION 1.0, 29 MAY 2018

DAIICHI SANKYO

INVESTIGATOR AGREEMENT

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Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo Co., LTD representative listed below.

PPD

Print Name | **Signature**

Clinical Study Lead/ Clinical Scientist

Title | **Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name | **Signature**

Title | **Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

EudraCT Number:	Not applicable.
IND Number:	Not applicable.
Protocol Number:	DS1205-A-J102
Study drug:	DS-1205c
CCI [redacted]	CCI [redacted]
Study Title:	A Multicenter, Open-Label Phase 1 Study of DS-1205c in Combination with Gefitinib in Subjects with Metastatic or Unresectable EGFR-Mutant Non-Small Cell Lung Cancer
Study Phase:	Phase 1
Indication Under Investigation:	Metastatic or unresectable epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) subjects who are threonine 790 to methionine (T790M) mutation-negative after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.
Study Objectives:	**Dose Escalation** Primary Objective • To assess the safety and tolerability and to determine the recommended dose for expansion (RDE) of DS-1205c when combined with gefitinib in metastatic or unresectable EGFR-mutant NSCLC subjects who are T790M mutation-negative after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib Secondary Objectives • To characterize the pharmacokinetics (PK) of DS-1205a (free form of DS-1205c) when DS-1205c is administered alone; and of DS-1205a and gefitinib when DS-1205c is administered in combination with gefitinib • To investigate the antitumor activity of DS-1205c in combination with gefitinib Exploratory Objectives

- To evaluate the effect on corrected QT interval (QTc) when DS-1205c is administered alone or in combination with gefitinib
- To identify biomarkers that correlate with efficacy or toxicity to DS-1205c in combination with gefitinib
- To assess changes in the profile of EGFR mutations and/or other genes in cell-free DNA (cfDNA) during treatment with DS-1205c in combination with gefitinib
- To conduct metabolite analysis of DS-1205c

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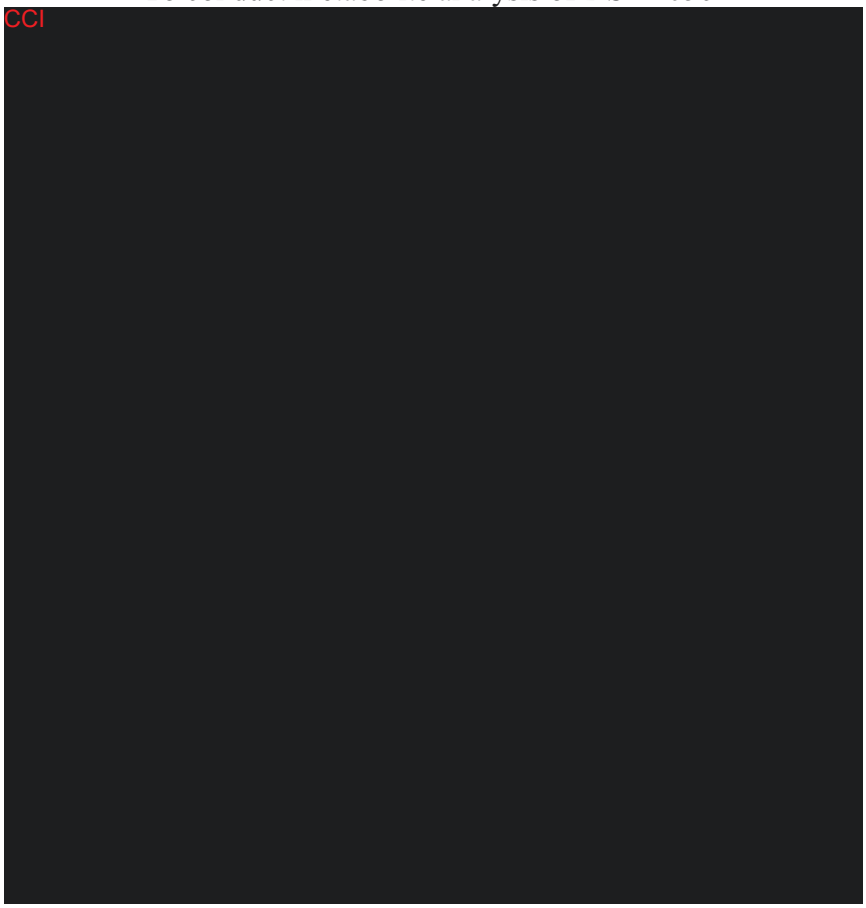

Study Design:	This is a multi-center, open-label, Phase 1 study of DS-1205c in combination with gefitinib in metastatic or unresectable EGFR-mutant NSCLC subjects who are T790M mutation-negative, after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib. This study has 2 parts: Dose Escalation and Dose Expansion. **Dose Escalation**

Dose Escalation consists of a DS-1205c monotherapy run-in period (Cycle 0) followed by combination treatment of DS-1205c and gefitinib (Cycle 1 and beyond).

Subjects will report to the clinic the morning of Cycle 0, Day 1 to obtain a baseline series of electrocardiograms (ECGs). Subjects must have taken their final dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib 1 day prior to breakfast in clinic on Cycle 0, Day 1. ECGs will be obtained at specified time points over a 8-hour period. During a 7-day run-in period (Cycle 0), subjects will be administered DS-1205c orally twice daily (BID). Safety, PK, vital sign, and ECG assessments will be obtained over the 7-day period.

Cycle 1, Day 1: Following the end of the 7-day run-in period, DS-1205c will be administered orally BID in combination with gefitinib 250 mg administered orally once daily (QD), in 21-day cycles. See table below.

Dose Escalation Provisional Cohorts and Provisional Dosages

Cohort[a]	Cycle 0 Monotherapy (7-day cycle)	Cycle 1 and Beyond Combination Therapy (21-day cycles)	
	DS-1205c Dosage[b]	DS-1205c Dosage[b]	Gefitinib Dosage[c]
1	200 mg BID	200 mg BID	250 mg QD
2	400 mg BID	400 mg BID	250 mg QD
3	600 mg BID	600 mg BID	250 mg QD
4	800 mg BID	800 mg BID	250 mg QD

BID = twice daily; mg = milligrams; QD = once daily

a The second subject in each cohort should start dosing at least 24 hours after the initial dosing of the first subject. The cohort numbers in this table do not denote actual order of dose transition on the trial.

b Administer with a meal, with 240 mL of water. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes, and DS-1205c should be taken immediately after meal completion. Doses of DS-1205c should be taken approximately 12 hours apart.

c Co-administer with morning dose of DS-1205c.

	Dose escalation will be guided by the modified Continuous Reassessment Method (mCRM) using a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. In this method, a decision to escalate to the next cohort is based on review of all subjects who have completed the dose-limiting toxicity (DLT)-evaluation period. The DLT-evaluation period is defined as the 7 days of Cycle 0 plus the 21 days of Cycle 1 (28 days total). A DLT-evaluable subject is defined as a subject who has received DS-1205c and EITHER has completed minimum safety evaluation requirements over the DLT-evaluation period OR has experienced a DLT during the DLT-evaluation period. The RDE will be decided based on an overall assessment of available safety and tolerability data from Cycle 1 and beyond, and all available PK, biomarker, and tumor response data. Dose Escalation will be stopped if any of the following occur: (a) at least 6 evaluable subjects have been enrolled at the RDE with at least 18 evaluable subjects in total enrolled in Dose Escalation, or (b) at least 9 evaluable subjects have been enrolled at a particular dose level, the model recommends continuing at the same dose level, and the posterior probability of the DLT rate falling within the target DLT interval is ≥ 50%, or (c) the starting dose is too toxic. CCI 
Study Duration:	**Dose Escalation**

	• Enrollment is planned to occur over approximately 12 months. • Treatment and follow-up will be completed when all subjects have either discontinued study treatment or completed last study visit. CCI [redacted] The number of treatment cycles is not fixed in this study. Subjects will continue study treatment until withdrawal of consent, progressive disease (PD), or unacceptable toxicity for all subjects in Dose Escalation and Dose Expansion.
Study Sites and Locations:	Approximately 20 clinical sites within Japan. Additional sites and countries may be added as needed.
Subject Eligibility Criteria:	Key Inclusion Criteria: 1. Has histologically or cytologically documented adenocarcinoma NSCLC. 2. Has locally advanced or metastatic NSCLC, not amenable to curative surgery or radiation. 3. Has acquired resistance to EGFR TKI according to the Jackman criteria (PMID: 19949011): a. Historical confirmation that the tumor harbors an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q), OR b. Has experienced clinical benefit from an EGFR TKI, followed by systemic progression (Response Evaluation Criteria in Solid Tumors [RECIST version 1.1] or World Health Organization [WHO]) while on continuous treatment with an EGFR TKI. 4. Is currently receiving and able to interrupt gefitinib or discontinue erlotinib, afatinib, dacomitinib, or osimertinib. 5. Has been receiving gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib for at least 6 weeks with well-controlled related toxicities less than Grade 3 in severity at the time of screening period. Subjects

who have been receiving gefitinib must be taking gefitinib at a dose of 250 mg/day.

6. Has radiological documentation of disease progression while receiving continuous treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.
7. Has at least one measurable lesion per RECIST version 1.1.
8. Is willing to provide archival tumor tissue from a biopsy performed after progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib OR has at least one lesion, not previously irradiated, amenable to core biopsy and is willing to undergo screening tumor biopsy.
9. Demonstrates absence of EGFR T790M mutation in tumor tissue since progression during gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib treatment.
10. Has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, with no deterioration over the previous 2 weeks.

Key Exclusion Criteria:

1. Has any evidence of small cell histology, or combined small cell and non-small cell histology, in original tumor biopsy or in screening biopsy performed since progression.
2. Has previously documented evidence of anaplastic lymphoma kinase (ALK) fusion, ROS proto-oncogene 1 (ROS1) fusion, BRAF V600E mutation, rearranged during transfection (RET) rearrangement, human epidermal growth factor receptor 2 (HER2) mutation, or MET exon 14 skipping mutation. No new testing for these genomic alterations is required for Screening.
3. Has received treatment with any of the following:
    a. Any cytotoxic chemotherapy, immune checkpoint inhibitor therapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), within 14 days of the first dose of study treatment.
    b. Immune checkpoint inhibitor therapy within 30 days of first dose of study treatment.

c. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment.

d. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks, or palliative radiation therapy within 2 weeks of the first dose of study drug treatment.

4. Has history of other active malignancy within 3 years prior to enrollment, except:
   a. Adequately treated non-melanoma skin cancer OR
   b. Superficial bladder tumors (Tumor stage “a” [Ta], Tumor stage “is” [Tis], Tumor stage “1” [T1]) OR
   c. Curatively treated in situ disease OR
   d. Low-risk non-metastatic prostate cancer (with Gleason score < 7 on antiandrogen therapy)
5. Has spinal cord compression or clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy).
6. Presence of retinal disease in the eye that is not due to neovascular age-related macular degeneration (nAMD; eg, significant diabetic retinopathy, glaucomatous retinal atrophy, retinal detachment).
7. Has history of myocardial infarction within the past 6 months.
8. Has symptomatic congestive heart failure (New York Heart Association [NYHA] Classes II IV), unstable angina, or cardiac arrhythmia requiring antiarrhythmic treatment.

	9. Has left ventricular ejection fraction (LVEF) < 45% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan. 10. Has any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval > 250 milliseconds (ms). 11. Has a mean corrected QT interval using Fridericia's correction (QTcF) prolongation >470 ms for females and >450 ms for males in three successive Screening measurements. 12. Unable or unwilling to discontinue concomitant use of drugs that are known to prolong the QT interval. 13. Has any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as congenital long QT. syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives. 14. Has a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required corticosteroid treatment, has current ILD/pneumonitis, or has suspected ILD/pneumonitis which cannot be ruled out by imaging at screening. 15. Has history of pancreatitis within the past 6 months.
Dosage Form and Route of Administration:	DS-1205c is supplied as 200 mg capsules, white opaque with red lines, packaged in high-density polyethylene (HDPE) bottles of 32 capsules. DS-1205c will be taken orally BID with doses taken approximately 12 hours apart. DS-1205c should be administered or taken with a meal, with 240 mL of water. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS-1205c should be taken immediately after meal completion. Gefitinib is prescribed as 250 mg tablets. Beginning with Day 1 of Cycle 1, gefitinib will be co-administered orally QD with the morning dose of DS-1205c.
Study Endpoints:	**Dose Escalation** Primary Endpoints (ie, Primary Outcome Measures):

- To determine the safety and tolerability of DS-1205c in combination with gefitinib, the endpoints will include DLTs, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examination findings (including ECOG PS), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters (including the change-from-baseline ECG parameters: heart rate [HR]; PR; QTcF; and QRS intervals [ΔHR, ΔPR, ΔQTcF, and ΔQRS]), ECHO or MUGA findings, and radiographic findings. Adverse events (AEs) and abnormal laboratory findings will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Secondary Endpoints (ie, Secondary Outcome Measures)

- Cycle 0: To assess PK of DS-1205a, the endpoints will include plasma concentration of DS-1205a versus time, and maximum plasma concentration (Cmax), the actual sampling time to reach Cmax (Tmax), trough plasma concentration (Ctrough), area under the plasma concentration-time curve during a dosing interval (AUCtau), and other PK parameters, as appropriate.
- Cycle 1 and beyond: To assess the PK of DS-1205a, and gefitinib, the endpoints will include plasma concentration of DS-1205a, and gefitinib versus time, and maximum observed analyte concentration during a dosing interval (Tau) (Cmax), Tmax, Ctrough, AUCtau, and other PK parameters, as appropriate.
- The efficacy endpoint is the objective response rate (ORR, the number of subjects with best objective response [complete response (CR) or partial response (PR), divided by the number of subjects in the analysis population]), as determined by Investigator assessment based on RECIST version 1.1. Additional efficacy endpoints are duration of response (DOR, the time from documentation of tumor response [either CR or PR] to disease progression), disease control rate (DCR, the sum of CR rate, PR rate,

and stable disease (SD) rate), progression-free survival (PFS), time to response (TTR) and overall survival (OS).

Exploratory Endpoints (ie, Exploratory Outcome Measures)

- Biomarkers measured in tumor specimens (eg, AXL immunohistochemistry [IHC], AXL and AXL pathway genes measured by NanoString multiplex RNA and/or other methods, and/or protein analysis) that correlate with response or toxicity to DS-1205c in combination with gefitinib will be assessed.
- Biomarkers measured in plasma (eg, cfDNA) that correlate with response or toxicity to DS-1205c in combination with gefitinib will be assessed.
- EGFR mutation(s) or mutations in other genes in cfDNA during treatment with DS-1205c in combination with gefitinib will be assessed.
- To assess change-from-baseline QTcF (ΔQTcF) when DS-1205c is administered alone or in combination with gefitinib.

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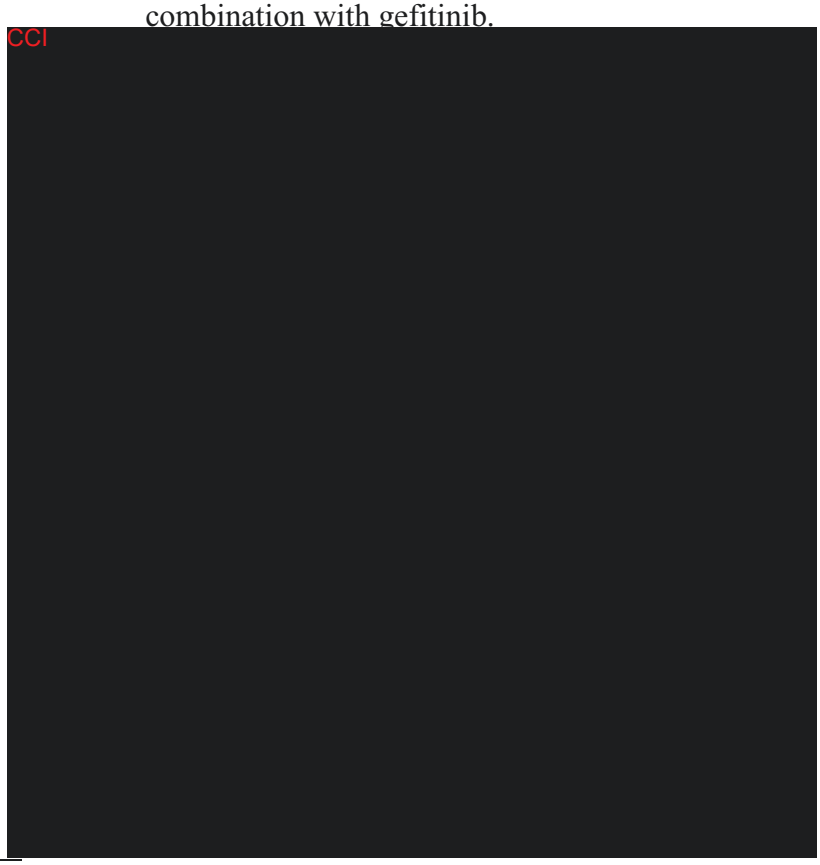

	CCI [redacted]
Planned Sample Size:	**Dose Escalation** Approximately 18 subjects will be enrolled. CCI [redacted]
Statistical Analyses:	The final efficacy analysis will occur after all subjects have either discontinued the study or completed last study visit or contact. Safety Analyses: The safety profile will be based on SAEs, TEAEs, Aes, standard clinical laboratory measurements, vital sign measurements, ECG parameters, physical examination findings, ECHO/MUGA findings, and ophthalmologic findings. Aes and abnormal laboratory values will be graded according to the NCI-CTCAE version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In Dose Escalation, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized. Clinical interpretation of ECGs will be summarized descriptively. Pharmacokinetic (PK) Analyses: PK parameters for each subject will be estimated using non-compartmental analysis (NCA). Descriptive statistics will be provided for all plasma concentration

data by analyte/dose/study day/time and for each PK parameter by analyte/dose/study day, as appropriate.

Efficacy Analyses:

The efficacy analysis will be performed for the subjects who received at least one dose of study drug by dose level within each part and overall. The analysis will be based on subjects dosed at the level of RDE at both the dose escalation part and the dose expansion part. Analyses will be performed for each dose level. Subjects with unknown or missing response will be treated as non-responders. The estimate of ORR will be reported as a summary statistic. The DCR will be reported as a summary statistic, and point estimates and 2-sided 95% exact binomial confidence intervals (CIs) will be provided. Time to event variables including DOR, TTR, PFS, and OS will be summarized with median event times with 2-sided 95% CI using the Kaplan-Meier method.

Biomarker Analyses:

Tissue biopsy obtained from a site of PD and prior to study treatment will be analyzed for AXL expression using IHC, and the mRNA of several hundred genes will be measured using NanoString or other method(s). Biomarkers will be summarized using descriptive and correlative analyses, as appropriate.

Exploratory Analyses:

The Concentration-QTc analysis plan will be presented in a separate document.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
Δ	change from baseline
µM	micromolar
AC	Adjudication Committee
ADL	activities of daily living
AE	adverse event
AESI	adverse event(s) of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc antibody	anti-hepatitis B core antibody
anti-HBs antibody	anti-hepatitis B surface antibody
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time 0 to 24 hours
AUCtau	area under the plasma concentration-time curve during a dosing interval
AXL	receptor tyrosine kinase
BID	twice daily
BLRM	Bayesian logistic regression model
BUN	blood urea nitrogen
CAP	College of American Pathologists
cDNA	complementary DNA
cfDNA	cell-free DNA
CHL	Chinese hamster lung
CI	confidence interval
CK	creatine kinase
Cmax	maximum plasma concentration
Ctrough	trough plasma concentration
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
CYP	cytochrome P450

ABBREVIATION	DEFINITION
DCR	disease control rate
dL	deciliter(s)
DLT	dose-limiting toxicity
DOR	duration of response
DS-1205a	*N*-[4-(2-Amino-5-{4-[(2*R*)-1,4-dioxan-2-ylmethoxy]-3-methoxyphenyl}pyridin-3-yl)-3-fluorophenyl]-5-methyl-4'-oxo-1'-(tetrahydro-2*H*-pyran-4-ylmethyl)-1',4'-dihydro-2,3'-bipyridine-5'-carboxamide, free form of DS-1205c
DS-1205b	1 4/5 sulfate trihydrate of DS-1205a
eCRF	electronic Case Report Form
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
ETV	estimated tumor volume
EWOC	escalation with overdose control
FAS	full analysis set
FDA	Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxine
g	gram(s)
G719X	glycine 719 to alanine, cysteine, aspartate, or serine (mutation in EGFR)
GAS6	growth arrest-specific gene 6
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practic
h	hour
Hb	hemoglobin
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2

ABBREVIATION	DEFINITION
hERG	human ether-à-go-go related gene
hGAS6	human growth arrest-specific gene 6
HGFs	hematopoietic growth factors
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	heart rate
HRCT	high resolution computed tomography
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Council of Medical Journal Editors
IEC	Institutional Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
ILD AC	Interstitial Lung Disease Adjudication Committee
IND	Investigational New Drug
INN	international non-proprietary name
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
kg	kilogram(s)
L858R	leucine 858 to arginine (mutation in EGFR)
L861Q	leucine 861 to glutamine (mutation in EGFR)
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MC	methylcellulose
mCRM	modified Continuous Reassessment Method
MedDRA	Medical Dictionary for Regulatory Activities
MET	hepatocyte growth factor receptor
µg	microgram
min	minute
mL	milliliter

ABBREVIATION	DEFINITION
MRI	magnetic resonance imaging
mRNA	messenger RNA
ms	millisecond(s)
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
nAMD	neovascular age-related macular degeneration
NCI	National Cancer Institute
NE	not evaluable
NGS	next-generation DNA sequencing
NIH3T3-AXL	AXL cDNA-transfected NIH3T3
nM	nanomolar
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic(s)
PMID	PubMed Unique Identifier
PR	partial response
PR interval	time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex (onset of ventricular depolarization) in the ECG
PS	Performance Status
PT	Preferred Term
PT-INR	prothrombin time-International Normalized Ratio
aPTT	activated partial thromboplastin time
QA interval	time between the onset of the Q wave in the ECG and the beginning of the rise in the following arterial blood pressure pulse
QD	once daily
QRS interval	duration of the QRS complex of the ECG
QT interval	time from the beginning of the Q wave to the end of the T wave in the ECG
QTc	corrected QT interval

ABBREVIATION	DEFINITION
QTcF	corrected QT interval using Fridericia's correction
radio-HPLC	radio-high-performance liquid chromatography
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1
RR interval	time from the peak of one QRS complex to the peak of the next in the ECG
SAE	serious adverse event
SAP	statistical analysis plan
SAVER	Serious Adverse Event Report
SD	stable disease
SD	standard deviation
SID	subject identification (number)
SOC	System Organ Class
STD_{10}	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reaction
T1	Tumor stage "1"
t1/2	terminal elimination half-life
T3	triiodothyronine
T4	thyroxine
T790M	threonine 790 to methionine (mutation in EGFR)
Ta	Tumor stage "a"
TAM	TYRO-3, AXL, and MER
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TGIn	tumor growth inhibition by net
Tis	Tumor stage "is"
TK	toxicokinetics
TKI	tyrosine kinase inhibitor
Tmax	time to reach Cmax
TSH	thyroid stimulating hormone
TTR	time to response
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal

ABBREVIATION	DEFINITION
US	United States
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Data Summary

1.1.1. Study Drug

1.1.1.1. Name

DS-1205c

1.1.1.2. Description

DS-1205c is a novel, specific, small-molecule inhibitor of the receptor tyrosine kinase AXL. CCI

[redacted]

1.1.1.3. Intended Use Under Investigation

DS-1205c will be evaluated in combination with gefitinib in subjects with metastatic or unresectable epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC) who are threonine 790 to methionine (T790M) mutation-negative after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.

1.1.2. Nonclinical Studies

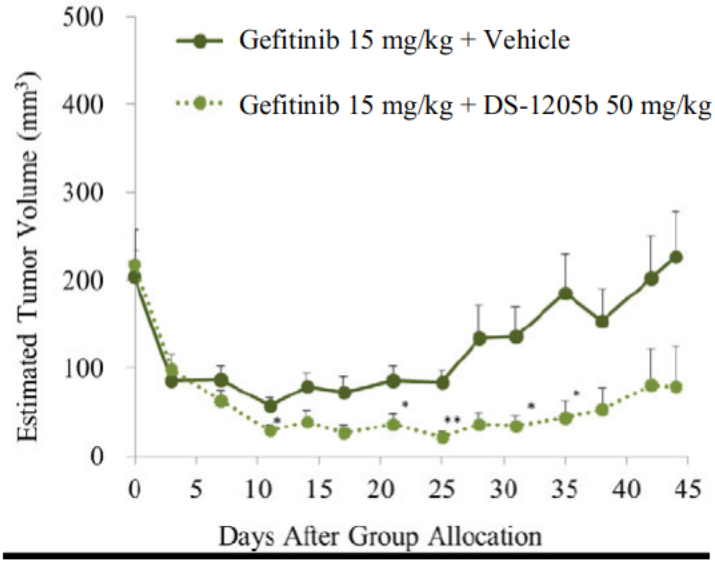
DS-1205b and DS-1205c were used in non-clinical studies as indicated below. In nonclinical studies, the doses and concentrations are expressed as those of DS-1205a (free base) unless otherwise stated.

1.1.2.1. Pharmacology

The inhibitory activity of DS-1205b on AXL kinase receptor phosphorylation in NCI-H1299 and AXL cDNA-transfected NIH3T3 (NIH3T3-AXL) cell lines was determined after growth arrest-specific gene 6 (GAS6) stimulation. Cells were pre-treated with DS-1205b and then stimulated with recombinant human growth arrest-specific gene 6 (hGAS6) receptor ligand, and the degree of endogenous AXL phosphorylation was quantified. DS-1205b showed potent concentration-dependent inhibition of AXL kinase receptor phosphorylation in NCI-H1299 and NIH3T3-AXL cells, with half-maximal inhibitory concentration (IC_{50}) values of 2.8 nM and 3.7 nM, respectively.

An in vivo study evaluated the delay effect of DS-1205b on the acquired resistance of gefitinib in nude mice subcutaneously inoculated with human NSCLC cell line HCC827. The effects of gefitinib and DS-1205b on estimated tumor volume (ETV) are presented in Figure 1.1. Groups of mice were administered either gefitinib 15 mg/kg QD combined with vehicle (0.5% methylcellulose [MC] 400) BID, or gefitinib 15 mg/kg QD combined with DS-1205b 50 mg/kg BID in accordance with a 5 days on/2 days off schedule. The effects of DS-1205b on the ETV are presented in Figure 1.1. DS-1205b showed an acquired-resistant delay effect of gefitinib on the ETV significantly ($P < 0.05$ on Days 11, 21, 31, and 35 or $P < 0.01$ on Day 25) with no remarkable body weight loss and abnormal clinical sign.

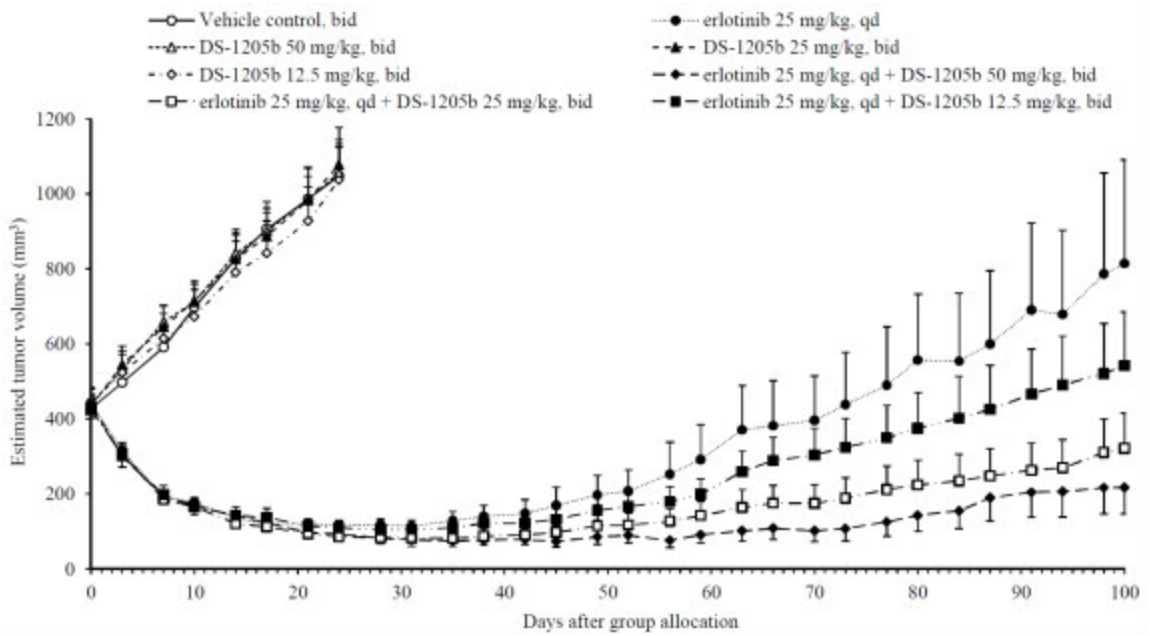
Figure 1.1: Effects of Gefitinib and DS-1205b on Estimated Tumor Volume in HCC827-Bearing Nude Mice



Data points indicate mean + standard error (n =5 for gefitinib and vehicle, n = 4 for gefitinib and DS-1205b). **: $P < 0.01$, *: $P < 0.05$, vs. gefitinib + vehicle by student's t-test.

An in vivo study evaluated the delay effect of DS-1205b on the acquired resistance of erlotinib in nude mice subcutaneously inoculated with human NSCLC cell line HCC827. The effects of erlotinib and DS-1205b on ETV are presented in Figure 1.2. Groups of mice were administered either erlotinib 25 mg/kg QD, or DS-1205b (12.5, 25, or 50 mg/kg BID), or erlotinib 25 mg/kg QD combined with DS-1205b (12.5, 25, or 50 mg/kg BID). For some groups, observation was undertaken until ETV reached 1000 mm^3 (Day 24); for other groups, observation was extended to Day 100. The mean ETVs on Day 100 for groups receiving erlotinib combined with DS-1205b at 50, 25, or 12.5 mg/kg BID were 216.8, 321.0, and 541.7 mm^3, respectively, compared to group 2 (erlotinib 25 mg/kg QD) with ETV of 814.5 mm^3. Significantly low values from the erlotinib group were found in the erlotinib combined with high dose DS-1205b groups on Days 59 to 80, 98 and 100 (P 0.0257 to 0.0469). DS-1205b showed a delay effect on ETV in a dose-dependent trend and significantly enhanced the antitumor effect of erlotinib at the dose of 50 mg/kg BID.

Figure 1.2: Effects of Erlotinib and DS-1205b on Estimated Tumor Volume in HCC827-Bearing Nude Mice

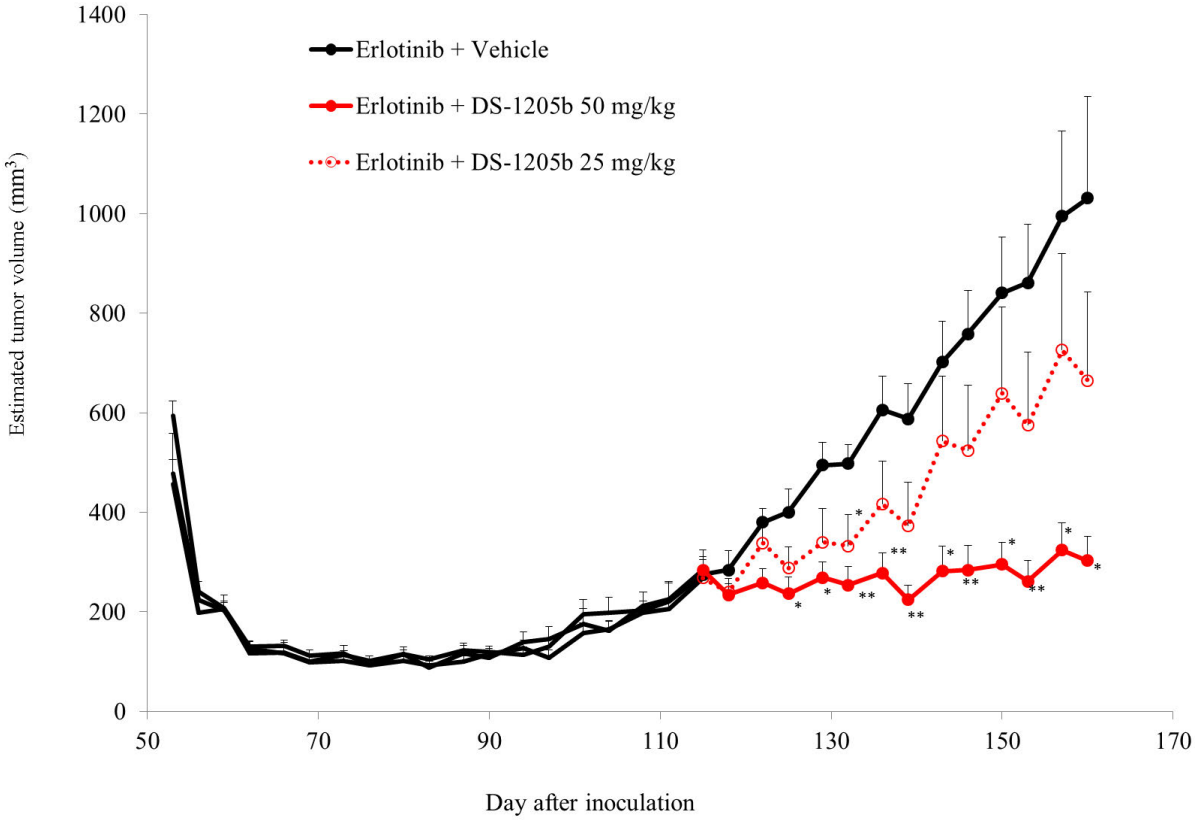


Data points indicate mean ± SD (N = 8).
No significant difference from the erlotinib 25 mg/kg, QD group was found in the erlotinib 25 mg/kg, QD + DS-1205b 25 mg/kg, BID and erlotinib 25 mg/kg, QD + DS 1205b 12.5 mg/kg, BID groups (Dunnett's test).
A significantly low value from the erlotinib 25 mg/kg, QD group was found in the erlotinib 25 mg/kg, QD + DS-1205b 50 mg/kg, BID group on Days 59 to 80, 98 and 100 (P = 0.0257 to 0.0469; Dunnett's test).
A significantly low value from the vehicle control, BID group was found in the erlotinib 25 mg/kg, QD group on Days 3 to 24 (P = 0.0021 on Day 3, P = 0.0000 on Days 7 to 24; Student's t test).
No significant difference from the vehicle control, BID group was found in the DS-1205b groups (Dunnett's test).
A significantly low value from the vehicle control, BID group was found in the erlotinib 25 mg/kg, QD + DS-1205b 50 mg/kg, BID group on Days 3 to 24 (P = 0.0003 on Day 3, P = 0.0000 on Days 7 to 24; Dunnett's test).
A significantly low value from the vehicle control, BID group was found in the erlotinib 25 mg/kg, QD + DS-1205b 25 mg/kg, BID group on Days 3 to 24 (P = 0.0005 on Day 3, P = 0.0000 on Days 7 to 24; Dunnett's test).
A significantly low value from the vehicle control, BID group was found in the erlotinib 25 mg/kg, QD + DS-1205b 12.5 mg/kg, BID group on Days 3 to 24 (P = 0.0003 on Day 3, P = 0.0000 on Days 7 to 24; Dunnett's test).

DS-1205b effect on the acquired resistance of erlotinib in an in vivo study in nude mice subcutaneously inoculated with the human EGFR-mutant NSCLC cell line HCC827 was also examined. Erlotinib resistant tumors were generated in female CanN.Cg-Foxn1nu/CrlCrlj [Foxn1nu/Foxn1nu] mice by subcutaneous inguinal inoculation of HCC827 human NSCLC cells, followed by repeated erlotinib daily administration (25 mg/kg) for approximately 9 weeks on a 5 days on/2 days off schedule. After generation of mice bearing erlotinib-resistant tumors, DS-1205b was given twice daily at doses of 25 or 50 mg/kg for approximately 7 weeks, on the days of erlotinib administration. The measurements were further continued until the mean ETV of

vehicle-treated group reached a size not exceeding 1000 mm^3. The effects of DS-1205b on tumor growth are demonstrated in Figure 1.3. The additional treatment of DS-1205b recovered the antitumor effect of erlotinib, when DS-1205b was given with twice daily administration for approximately 7 weeks with erlotinib. At doses of DS-1205b 50 mg/kg and 25 mg/kg, the tumor growth inhibition by net (TGIn) was 97% and 47% respectively at the end of administration, and a significant antitumor effect was seen at 50 mg/kg (*P* 0.0100). DS-1205b recovered antitumor activity of erlotinib in a dose-dependent manner, which was confirmed by hypothesis testing of Spearman's rank correlation coefficient (*P* 0.0002). There were no mice with severe body weight loss, and no death or abnormal signs were observed in this study.

Figure 1.3: Effects of Erlotinib and DS-1205b Using Acquired Erlotinib-Resistance Subcutaneous Tumor Model of HCC827



The HCC827 cells were inoculated subcutaneously into the inguinal region of female nude mice at 4 × 10^6 cells/mouse. From 53 days to 160 days after inoculation, erlotinib at the doses of 25 mg/kg was orally administered once daily (black solid line). Additionally, DS-1205b or vehicle was orally administrated twice daily from Day 116 to Day 160. The mean ETV of each group with the SE (N = 6) was plotted onto the graph.
** : $P < 0.01$, * : $P < 0.05$, vs. Erlotinib + vehicle-treated control by parametric Dunnett's test.

1.1.2.2. Safety Pharmacology

Safety pharmacology was assessed in a core battery of regulatory studies (International Council for Harmonisation [ICH] S7A and ICH S7B). In the in vitro human ether-à-go-go related gene (hERG) assay, DS-1205c inhibited hERG tail current, showing an

estimated IC_{50} value of 0.13 μM (equivalent to 0.09565 μg/mL of DS-1205a). However, in a study using telemetered male cynomolgus monkeys, there were no DS-1205c-related changes noted in systolic blood pressure, diastolic blood, mean blood pressure, heart rate [HR], electrocardiogram (ECG) parameters (PR, QRS, QT, corrected QT [QTc] intervals), and QA interval at doses of up to 1000 mg/kg. Furthermore, there were no effects in the ECG assessments at the same dose levels in the 4-week toxicity study in cynomolgus monkeys. Based on protein binding (approximately 99.4%), the IC_{50} value in the hERG assay was 4.2-fold higher than the unbound DS-1205a maximum plasma concentration (Cmax) value on Day 1 (approximately 0.02292 μg/mL) in the monkey 4-week repeated oral dose toxicity study at a dose of 1000 mg/kg, which was a lethal dose in males. Consequently, the possibility of unbound Cmax reaching hERG IC_{50} levels is considered to be low in clinical studies, however, careful ECG monitoring will be conducted during clinical trials.

1.1.2.3. Pharmacokinetics and Drug Metabolism

PK profiles were evaluated in the mouse and monkey during 4-week toxicity studies with DS-1205c. In mice, and where calculable, the terminal elimination half-life (t1/2) ranged between 2.28 and 4.97 hours. At the severely toxic dose in 10% of animals (STD_{10}) of 1000 mg/kg/day in mice, Cmax and area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{0\ 24h}$) mean values were 17.8 μg/mL and 219 μg•h/mL, respectively, in males, and 20.8 μg/mL and 240 μg•h/mL, respectively, in females, on Day 28. In monkeys, time to reach Cmax (Tmax) ranged between 4.0 and 6.0 hours after dosing in females, and between 2.0 and 6.0 hours after dosing in males. At the highest non-severely toxic dose (HNSTD) of 1000 mg/kg/day in females, Cmax and $AUC_{0\ 24h}$ mean values were 4.42 μg/mL and 63.3 μg•h/mL, respectively, on Day 28. At the HNSTD of 200 mg/kg/day in males, Cmax and $AUC_{0\ 24h}$ mean values were 2.85 μg/mL and 41.1 μg•h/mL, respectively, on Day 28. Within each species, there were no notable differences in exposure between males and females.

When DS-1205c was administered orally at doses of 100, 400, and 800 mg to male beagle dogs under fasted and fed conditions, the mean area under the plasma concentration-time curve (AUC) of DS-1205a was higher in fed dogs than in fasted dogs, suggesting a positive food effect on the absorption of DS-1205c. After oral administration of [^{14}C]DS-1205b to rats, the radioactivity was distributed to the whole body and eliminated rapidly from the tissues and had affinity to melanin. DS-1205a is highly protein bound (> 98.5%) in plasma from mouse, monkey, and human, and showed no concentration-dependency in all 3 species. The metabolism of DS-1205a was investigated in mouse, monkey, and human cryopreserved hepatocytes. A total of 10 metabolites were produced, all oxidative metabolites except for an *N*-glucuronide. The major metabolites were: in mouse, a mono-oxygenated form; in monkey, a mono-oxygenated form and a di-oxygenated form; in human, an *N*-glucuronide. On the radio-high-performance liquid chromatography (radio-HPLC) chromatogram for human samples *N*-glucuronide was the only quantifiable metabolite and no human specific metabolite was detected. The primary uridine 5'-diphosphate-glucuronosyltransferase (UDP-glucuronosyltransferase [UGT]) isoform responsible for glucuronidation of DS-1205a was identified as UGT1A4, followed by UGT1A1. When incubated with

microsomes containing a recombinant human cytochrome P450 (CYP) isoform, [^{14}C]DS-1205a was metabolized by CYP3A4 and CYP3A5.

1.1.2.4. Toxicology

In dose range finding studies of the 4-week repeated oral dose toxicity study in 5 male mice with DS-1205a (0 [vehicle], 200, and 1000 mg/kg/day) and a single increasing oral dose (100 and 300 mg/kg) followed by 7-day repeated oral dose (1000 mg/kg/day) toxicity study in 2 cynomolgus monkeys (1 male and 1 female) with DS-1205b, no severe toxicity was observed at up to 1000 mg/kg/day.

Four-week oral toxicity (with toxicokinetics [TK] analysis) studies with daily dosing of DS-1205c were conducted in mice and cynomolgus monkeys under compliance with the Good Laboratory Practice (GLP).

In mice (at doses of 100, 300, and 1000 mg/kg/day), the dose level of 1000 mg/kg/day caused mortality in 2 males but was well tolerated in all other animals. In clinical pathology, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and glutamate dehydrogenase (GLDH) activity were observed in males at ≥ 300 mg/kg/day and in females at 1000 mg/kg/day, with females more affected in terms of severity, and increases in creatine kinase (CK) and lactate dehydrogenase (LDH) activity were also observed in females at ≥ 300 and 1000 mg/kg/day, respectively. There were histopathological findings in the pancreas at ≥ 100 mg/kg/day, spleen and liver at 1000 mg/kg/day in both sexes, and an increased liver weight in males at 1000 mg/kg/day. All of the DS-1205c-related findings reversed after a 4-week treatment-free period, and the STD_{10} was thus 1000 mg/kg/day in males and females. The STD_{10} of 1000 mg/kg/day corresponded to Cmax and $AUC_{0\ 24h}$ mean values of 17.8 µg/mL and 219 µg·h/mL, respectively, in males, and Cmax and $AUC_{0\ 24h}$ mean values of 20.8 µg/mL and 240 µg·h/mL, respectively, in females, on Day 28.

In cynomolgus monkeys (at doses of 40, 200, and 1000 mg/kg/day), all 5 males given 1000 mg/kg/day were either found dead (1 animal) or prematurely sacrificed (including 2 moribund animals). The dead and moribund-sacrificed animals showed severe clinical signs including decreased activity, prostration and cold to touch, and severe degenerative changes in the kidneys; in animals sacrificed in extremis, there were also increases in blood urea nitrogen (BUN) and creatinine. In these animals, DS-1205c-related histopathological findings were observed in the heart, stomach, duodenum, pancreas, lymphoid organs, and liver. In other clinical pathology parameters, prematurely-sacrificed animals showed increases in white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and large unstained cell, and increases in ALT, AST, GLDH, LDH, CK, and triglycerides. In sacrificed animals on schedule including female given 1000 mg/kg/day, there were instances of pale or white feces and occasional vomit. There were minimal increases in ALT activity at ≥ 200 mg/kg/day, and decreases in spleen and thymus weight in males at 200 mg/kg/day. In females, there was a dose related increase in liver weight, and a decrease in thyroid weight at 1000 mg/kg/day. At the end of the treatment-free period, the observed clinical signs and the minimal increases in ALT activity completely recovered; a decrease in thymus weight in males at 200 mg/kg/day was still present but showed tendency toward recovery. On this basis, the

HNSTD was considered to be 200 mg/kg/day in males and 1000 mg/kg/day in females. The HNSTD of 200 mg/kg/day in males corresponded to Cmax and $AUC_{0\ 24h}$ mean values of 2.85 µg/mL and 41.1 µg·h/mL, respectively, on Day 28, and the HNSTD of 1000 mg/kg/day in females corresponded to Cmax and $AUC_{0\ 24h}$ mean values of 4.42 µg/mL and 63.3 µg·h/mL, respectively, on Day 28.

In an in vitro bacterial reverse mutation study, DS-1205c showed no mutagenic activity. In both an in vitro micronucleus study in Chinese hamster lung (CHL) cells and an in vivo bone marrow micronucleus studies in rats, DS-1205c showed no induction of chromosome aberrations. Therefore, DS-1205c was considered to have no genotoxic potential.

Additional data describing the use of DS-1205c in nonclinical studies are available in the current Investigator's Brochure (IB).[1]

1.1.3. Clinical Experience

There are no clinical data available for DS-1205c to date; periodic updates of clinical experience will be included in the Investigator's Brochure (IB).[1]

1.2. Background

Lung cancer is the leading cause of cancer-related death worldwide.[2] In addition, lung cancer is the second most commonly diagnosed cancer, with estimated 2.2 million new cases and 1.6 million deaths per year.[3]

1.2.1. Metastatic or Unresectable EGFR-Mutant NSCLC

EGFR-mutant NSCLC represents an important subtype of lung cancer where significant advances have been made in first-line treatment but where limited options are available in subsequent-line treatment.

It has been well established through multiple large Phase 3 studies that EGFR tyrosine kinase inhibitors (TKIs) represent the first-line treatment of choice in NSCLC with EGFR-activating mutations.[4, 5, 6, 7, 8, 9, 10] Gefitinib, erlotinib, and afatinib (and more recently, osimertinib)[11] have demonstrated significant improvements in objective response rate (ORR) and progression-free survival (PFS) compared to chemotherapy.

Despite the often dramatic responses to these agents, however, patients ultimately develop resistance to these treatments, usually within a year. Biopsies performed upon disease progression (which have evolved to be considered part of the standard of clinical care in the treatment of these patients) have revealed several molecular mechanisms of resistance.[12] Over half of these patients develop a secondary mutation in EGFR exon 20, T790M, in the adenosine triphosphate (ATP)-binding site.[13] Patients lacking this resistance mutation have exhibited other mutations, amplifications in the EGFR gene, activation or up-regulation of other "bypass track" signaling pathways, and phenotypic alterations including small cell lung cancer transformation and NSCLC epithelial-to-mesenchymal transition.[14]

Until recently, the standard of care treatment in the second-line setting has been chemotherapy. The retrospective Phase 3 NEJ002 study, which compared gefitinib with carboplatin plus paclitaxel, demonstrated[15] that second-line, platinum-based chemotherapy followed at progression by gefitinib was similar to first-line, platinum-based chemotherapy in terms of relative risk (RR) (partial response [PR] with chemotherapy second-line vs. first-line treatment: 25.4% vs. 30.7%; odds ratio 1.45; 95% CI [0.75, 2.81]; *P* 0.345) and overall survival (OS) (28.9 vs. 27.6 months; hazard ratio, 0.77; 95% CI [0.52, 1.14]; *P* 0.188), with no difference seen for the efficacy of second-line, platinum-based chemotherapy in the EGFR mutation subtype. Progression-free survival (PFS) was not evaluable in this study.

Patients with tumors that have acquired the T790M resistance mutation may now be treated with osimertinib, a third-generation EGFR TKI that specifically targets the T790M mutant-form of EGFR. In a pivotal Phase 1 study of EGFR-mutant NSCLC patients in the second-line setting, 127 T790M-positive subjects who could be evaluated for response demonstrated an ORR of 61% and median PFS of 9.6 months.[16]

For patients without documented T790M mutation, combination chemotherapy (as used in first-line NSCLC treatment) remains the standard treatment, particularly for patients who are symptomatic from progressive disease (PD); but again, these responses are generally not durable.[17] A number of other approaches have been explored with achievement of only incremental effectiveness,[18] as discussed below.

Changing to a second-generation TKI does not appear to confer significant benefit. Two Phase 2 trials have tested the efficacy of afatinib in patients with advanced NSCLC who progressed after one or two lines of chemotherapy and with at least 12 weeks of erlotinib and/or gefitinib. In the LUX-Lung 1 trial, where 585 patients were randomized to afatinib or placebo, a 2-month PFS improvement was seen with afatinib (3.3 vs. 1.1 months; $P < 0.0001$), without OS benefit (10.8 vs. 12.0 months; *P* 0.74).[19] The LUX-Lung 4 single-arm trial showed a median PFS of 4.4 months with afatinib in this pretreated population.[20] Neither of these trials supports switching to second-generation EGFR TKIs; instead, they support continuing inhibition of EGFR pathway beyond EGFR TKI progression. The combination of cetuximab and afatinib could be considered in fit patients (because of a relatively higher adverse event [AE] profile) following primary TKI and after subsequent chemotherapy, given a response rate of 35% (13 of 37) in T790M-negative patients.[21]

Tumor flare represents a significant phenomenon in EGFR-mutant NSCLC treated with TKI, whereby as many as 23% of patients may develop rapid growth of one or more tumor sites following withdrawal of TKI, and this may be associated with significant morbidity or even death. In a meta-analysis[22] the median time of tumor flare onset after TKI withdrawal was 8 days, with a range of 3 to 21 days. These and other observations have led to the recommendation that patients receiving treatment with TKI in the first-line setting and demonstrating progression by Response Evaluation Criteria in Solid Tumors (RECIST) may continue on their TKI and receive localized treatment (eg, radiotherapy or surgical therapy) as needed for site(s) of PD.[22]

Continuation of primary TKI does not appear to be indicated, however, in patients with EGFR-mutant NSCLC who experience progression on primary TKI and are given chemotherapy in the second-line setting. Recently updated OS results from the Phase 3 IMPRESS study[23] demonstrate that in 265 EGFR-mutant NSCLC patients who had developed acquired resistance to first-line gefitinib, median OS in the gefitinib plus chemotherapy (cisplatin/pemetrexed) arm was 13.4 months vs. 19.5 months with placebo plus chemotherapy (hazard ratio 1.44; *P* 0.016). A subgroup analysis stratifying by T790M status showed that of 247 patients for whom T790M status was available, the median PFS for the T790M mutation-positive subgroup was 4.6 vs. 5.3 months for the gefitinib and placebo groups, respectively (hazard ratio, 0.97; 95% CI [0.67, 1.42]; *P* 0.8829). Median PFS for the T790M mutation-negative subgroup was 6.7 vs. 5.4 months for the gefitinib and placebo arms, respectively (hazard ratio, 0.67; 95% CI [0.43, 1.03]; *P* 0.0745). These results suggest[24] that following acquired resistance to first-line gefitinib, for T790M-positive patients, gefitinib should not be continued when platinum-based doublet chemotherapy is available as second-line therapy. However, for plasma T790M-negative patients, the continuation of gefitinib in combination with platinum-based doublet chemotherapy may potentially offer some clinical benefit, but this requires further confirmation in a prospective randomized placebo-controlled study.

Immune checkpoint inhibitor therapies have been approved for treatment of advanced NSCLC in both the first- and second-line settings. Although patients with EGFR-mutant NSCLC are eligible to receive these therapies, data from several studies have not been powered to demonstrate a statistically significant benefit for any of these therapies compared to chemotherapy in EGFR-mutant patient subgroups. The meta-analysis of these therapies[25] from three large randomized trials comparing an immune checkpoint inhibitor to docetaxel in NSCLC patients has been conducted. In total, 1903 patients were randomized to receive an immune checkpoint inhibitor (nivolumab [n 292], pembrolizumab [n 691], or atezolizumab [n 144]) or docetaxel (n 776), and the EGFR mutation status was known for 1548 of these patients (81%). Treatment with an immune checkpoint inhibitor, compared with docetaxel, was associated with a 32% reduction in the risk for death in the intention-to-treat population (hazard ratio 0.68, 95% CI [0.61, 0.77], $P < 0.0001$; heterogeneity *P* 0.67). In the EGFR wild-type subgroup (n 1362), the pooled hazard ratio was 0.66 (95% CI [0.58, 0.76], $P < 0.0001$; heterogeneity *P* 0.96). In the EGFR-mutant subgroup (n 186), the pooled hazard ratio was 1.05 (95% CI [0.70, 1.55], $P < 0.81$; heterogeneity *P* 0.80). There was a statistically significant treatment-mutation interaction (*P* 0.03). Among the EGFR-mutant subgroup, there was no significant statistical heterogeneity in treatment effect: χ^2 0.46 (*P* 0.42) and I^2 0%. However, given the small sample sizes of EGFR-mutant subjects in these studies, the hypothesis that immune checkpoint inhibitor is not superior to chemotherapy in EGFR-mutant NSCLC is as yet unproven and is a subject of ongoing evaluation in the field.

Patients who experience transformation of tumor histology to small cell lung cancer are recommended to receive standard treatments for small cell lung cancer.[17] This transformation appears to occur with significant frequency (5 to 14%) in small series of EGFR-mutant NSCLC patients treated with TKI (reviewed in [26]). It remains unclear

whether this incidence of transformation is related primarily to the high frequency of serial biopsies in EGFR-mutant NSCLC or whether this is a consequence of genomic alterations in EGFR-mutant NSCLC, of TKI treatment, or both.

1.3. Study Rationale and Dose Selection

1.3.1. Study Rationale

In over half of patients with EGFR-mutant NSCLC acquire resistance to first or second generation TKIs (eg, gefitinib, erlotinib, or afatinib), is associated with the development of the secondary mutation in EGFR exon 20, T790M.[13] Among the remaining cases, a number of other proposed mechanisms, including the up-regulation of "bypass track" signaling pathways, may be responsible for treatment resistance. AXL expression was observed to be up-regulated in approximately 20% of EGFR-mutant NSCLC patients experiencing disease progression on erlotinib.[27,28]

Increased expression of AXL has been observed in EGFR-mutant NSCLC tumor biopsies obtained from patients with acquired resistance to TKIs.[28] As a member of the mammalian TYRO-3, AXL, and MER (TAM) receptor kinase family (named for its members TYRO3, AXL, and MER), AXL is a cell-surface transmembrane receptor containing regulated kinase activity within its cytoplasmic domain, and plays an important role in signal transduction in normal and malignant cells.[29,30] Overexpression or ectopic expression of TAM receptors is known to occur in a wide array of human cancers.[31] GAS6 is the major ligand for these TAM receptor tyrosine kinases and, in particular, is the sole ligand for AXL.[29] Its binding to the receptors promotes proliferation, survival, and migration of cancer cells in vitro.[30,32] Abnormal expression and activation of AXL can provide a survival advantage for certain cancer cells, and inhibition of AXL may enhance sensitivity of cancer cells to cytotoxic agents.[30]

DS-1205c is a novel, specific, small-molecule inhibitor of the receptor tyrosine kinase AXL, and is being developed by Daiichi Sankyo as an oral antitumor agent. Addition of DS-1205c restores TKI sensitivity in HCC827 (EGFR exon19deletion, T790M-negative) tumor xenograft models. Additionally, inhibition of acquired resistance to gefitinib following the addition of DS-1205c has been demonstrated in non-clinical studies.[1]

In summary, DS-1205c is hypothesized to show potential activity in combination with gefitinib in T790M mutation-negative EGFR-mutant NSCLC with a manageable safety profile.

1.3.2. Study Dose Setting

1.3.2.1. DS-1205c Starting Dose

The doses of DS-1205c selected for this study are based on nonclinical data and are expressed in doses of DS-1205a (free base). DS-1205c 200 mg capsules contain equivalent to 200 mg of DS-1205a (free form). Nonclinical data showed that a dose of 1000 mg/kg/day of DS-1205c was the STD_{10} in the mouse. The human equivalent dose (HED) for 1000 mg/kg, based on allometric scaling by surface area, is approximately 81.3 mg/kg, and using one-tenth of this value gives a dose of 8.1 mg/kg as the

recommended starting dose for the proposed clinical study. The value of 8.1 mg/kg is lower than an alternative starting dose (10.8 mg/kg) calculated using one-sixth of the HED for the HNSTD (200 mg/kg/day in males) in the cynomolgus monkey, and thus is considered to be the appropriate upper bound for a starting dose for clinical study in humans.[1] For a 60 kg human, the 8.1 mg/kg dose becomes 488 mg. Therefore, this study will use a starting dose of 400 mg per day of DS-1205c administered orally in 2 divided doses (200 mg twice daily [BID]).

1.3.2.2. Gefitinib Dosage

In this study, DS-1205c will be administered in combination with gefitinib (Iressa®). Open-label commercial supplies of gefitinib (Iressa®) will be used and reimbursed by the Sponsor. Gefitinib has been approved (Japan [Standard Commodity Classification Number: 874291], July 2002) for the treatment of patients with unresectable or recurrent NSCLC harboring EGFR mutations at a recommended dose of one 250 mg tablet administered orally once daily (QD).

1.4. Risks and Benefits for Study Subjects

1.4.1. Potential Risks Associated With DS-1205c

No safety information in humans is available.

In nonclinical toxicicty studies conducted in mice, elevations in clinical laboratories including ALT, AST, ALP GLDH, creatinine kinase (CK), and LDH. In cynomolgus monkeys, DS-1205c-related histopathological findings were observed in the heart, stomach, duodenum, pancreas, lymphoid organs, and liver. In other clinical pathology parameters, prematurely-sacrificed animals showed increases in white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and large unstained cell, and increases in ALT, AST, GLDH, LDH, CK, and triglycerides.

1.4.2. Potential Risks Associated With Gefitinib

Refer to the gefitinib package insert for detailed description of potential risks associated with gefitinib. As for potential risks overlapping with DS-1205c, hepatotoxicity has been reported with gefitinib. In subjects who received gefitinib in clinical trials with gefitinib,[33] 11.4% of subjects had increased ALT, 7.9% of subjects had increased AST, and 2.7% of subjects had increased bilirubin. Grade 3 or higher liver test abnormalities occurred in 5.1% (ALT), 3.0% (AST), and 0.7% (bilirubin) of those subjects. The incidence of fatal hepatotoxicity was 0.04%.

1.4.3. Pharmacokinetic Drug Interaction

In vitro metabolism studies using human hepatocytes indicated that major route of metabolism was *N*-glucuronidation. The primary UGT isoform responsible for glucuronidation of DS-1205a was suggested to be UGT1A4, and the second UGT1A1. In a study using microsomes containing recombinant human CYP isoforms, CYP3A4 was the main isoform and CYP3A5 was the minor isoform for the oxidation of DS-1205a.

DS-1205a did not show reversible inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, and DS-1205a did not show time-dependent inhibition of any CYP isoforms tested. In another in vitro study, DS-1205a had no induction effect on mRNA expression levels or specific enzyme activities of CYP3A4, CYP1A2, or CYP2B6.

In a study using Caco-2 cells, DS-1205a inhibited P-glycoprotein (P-gp)-mediated digoxin transport in vitro, with an IC_{50} of 1.20 μM. The clinical relevance of this inhibitory effect will depend on the intestinal and systemic concentration that DS-1205a will reach at the therapeutic dose, and on the concomitant drugs in target population.

1.4.3.1. Evaluation of the Potential for PK Interaction Effect on Gefitinib by DS-1205c

Gefitinib is extensively metabolized mainly via CYP3A4 and partially via CYP2D6.[34] However, since in vitro assessment shows that DS-1205c is neither an inhibitor nor an inducer of major CYP isoforms, the PK of gefitinib is unlikely to be significantly affected by co-administration of DS-1205c in humans. Although DS-1205c is an in vitro inhibitor of P-gp and gefitinib is an in vitro P-gp substrate, it is not expected that such inhibition will meaningfully impact the PK of gefitinib, given its high absorption and extensive metabolism. Based on mass balance study results of gefitinib, 80.8% of radioactivity was recovered in feces and 3.6% of radioactivity was recovered in urine. Only 4% of the dose recovered in feces was unchanged gefitinib following oral administration of [^{14}C]-gefitinib.[34]

1.4.3.2. Evaluation of the Potential for PK Interaction Effect on DS-1205c by Gefitinib

In vitro assessment using human hepatocytes showed that the major metabolic route of DS-1205a was *N*-glucuronidation, and oxidation metabolism was a minor route. The primary UGT isoform responsible for glucuronidation of DS-1205a was suggested to be UGT1A4, followed by UGT1A1, by in vitro studies. It is reported that gefitinib is unlikely to cause clinically significant DDI through inhibition of glucuronidation although gefitinib showed inhibition against UGT1A1, UGT1A7, UGT1A9, and UGT2B7 in vitro,[35] it is unlikely for gefitinib to cause clinically relevant increases in the exposure of DS-1205a given that *N*-glucuronidation of DS-1205a is primarily catalyzed by UGT1A4. Gefitinib is a CYP2D6 inhibitor in vivo, and it also inhibits CYP2C19 in vitro.[34] The oxidation metabolism of DS-1205a is catalyzed by CYP3A4 and CYP3A5, but not by CYP2C19 or CYP2D6. Therefore, co-administration of gefitinib is not expected to cause clinically significant effects on the PK of DS-1205c via UGT and CYP-related metabolism.

1.4.4. Potential Benefit Associated with DS-1205c

No efficacy information in humans is available.

Nonclinical studies have demonstrated the anti-tumor activity of DS-1205 in combination with gefitinib in xenograft models.[1] Based on the above rationale, and the nonclinical

data, DS-1205c in combination with gefitinib is hypothesized to show activity in EGFR-mutant NSCLC.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Dose Escalation

Primary Objective

- To assess the safety and tolerability and to determine the recommended dose for expansion (RDE) of DS-1205c when combined with gefitinib in metastatic or unresectable EGFR-mutant NSCLC subjects who are T790M mutation-negative after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib

Secondary Objectives

- To characterize the PK of DS-1205a (free form of DS-1205c) when DS-1205c is administered alone; and of DS-1205a and gefitinib when DS-1205c is administered in combination with gefitinib
- To investigate the antitumor activity of DS-1205c in combination with gefitinib

Exploratory Objectives

- To evaluate the effect on QTc when DS-1205c is administered alone or in combination with gefitinib
- To identify biomarkers that correlate with efficacy or toxicity to DS-1205c in combination with gefitinib
- To assess changes in the profile of EGFR mutations and/or other genes in cell-free DNA (cfDNA) during treatment with DS-1205c in combination with gefitinib
- To conduct metabolite analysis of DS-1205c

2.1.2. CCI

CCI [redacted]

2.2. Study Hypothesis

2.2.1. Dose Escalation

DS-1205c in combination with gefitinib will be safe and well tolerated in metastatic or unresectable EGFR-mutant NSCLC subjects who are T790M mutation-negative, after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.

2.2.2. CCI [redacted]

[redacted]

2.3. Study Endpoints

2.3.1. Dose Escalation

Primary Endpoints (ie, Primary Outcome Measures)

- To determine the safety and tolerability of DS-1205c in combination with gefitinib, the endpoints will include dose-limiting toxicities (DLTs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examination findings (including Eastern Cooperative Oncology Group [ECOG] performance status [PS]), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters (including the change-from-baseline ECG parameters: HR; PR; QTcF; and QRS intervals [ΔHR, ΔPR, ΔQTcF, and ΔQRS]), echocardiogram (ECHO)/multigated acquisition (MUGA) scan findings, and radiographic findings. Aes and laboratory findings will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Secondary Endpoints (ie, Secondary Outcome Measures)

- Cycle 0: To assess PK of DS-1205a, the endpoints will include plasma concentration of DS-1205a versus time, and Cmax, Tmax, trough plasma concentration (Ctrough), area under the plasma concentration-time curve during a dosing interval (AUCtau), and other PK parameters, as appropriate.

- Cycle 1 and beyond: To assess the PK of DS-1205a, and gefitinib, the endpoints will include plasma concentration of DS-1205a, and gefitinib versus time, and maximum observed analyte concentration during a dosing interval (Tau) (Cmax), Tmax, Ctrough, AUCtau, and other PK parameters, as appropriate.
- The efficacy endpoint is ORR: the number of subjects with best objective response (complete response [CR] or PR, divided by the number of subjects in the analysis population), as determined by Investigator assessment based on RECIST version 1.1. Additional efficacy endpoints are DOR (the time from documentation of tumor response [either CR or PR] to disease progression), disease control rate (DCR) (the sum of CR rate, PR rate, and stable disease [SD] rate), PFS, time to response (TTR); and OS.

Exploratory Endpoints (ie, Exploratory Outcome Measures)

- Biomarkers measured in tumor specimens that correlate with response or toxicity to DS-1205c in combination with gefitinib (eg, AXL immunohistochemistry [IHC], AXL and AXL pathway genes measured by NanoString multiplex RNA and/or other methods, and/or protein analysis) will be assessed.
- Biomarkers measured in plasma that correlate with response or toxicity to DS-1205c in combination with gefitinib (eg, cfDNA) will be assessed.
- EGFR mutation(s) or mutations in other genes in cfDNA during treatment with DS-1205c in combination with gefitinib will be assessed.
- To assess change-from-baseline QTcF (ΔQTcF) when DS-1205c is administered alone or in combination with gefitinib.

2.3.2. CCI

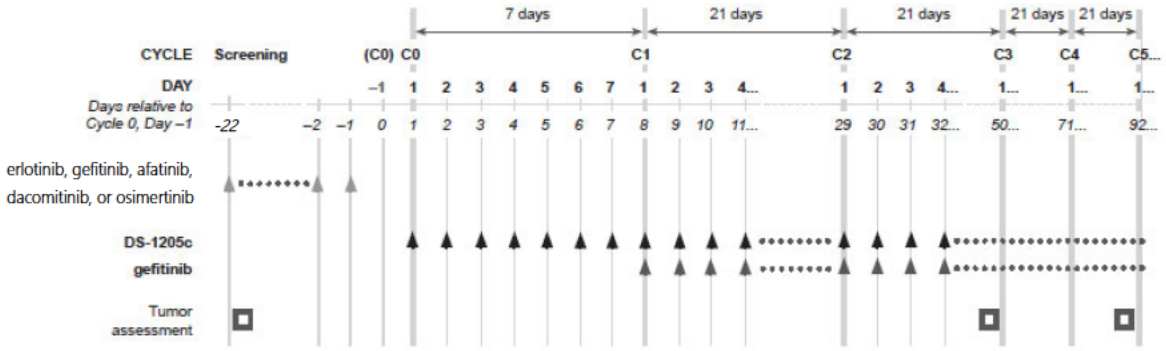

CCI

3. STUDY DESIGN

3.1. Overall Design Summary

This is a multi-center, open-label Phase 1 study of DS-1205c in combination with gefitinib in subjects ≥ 20 years old who have metastatic or unresectable EGFR-mutant NSCLC and are T790M mutation-negative after disease progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib. This study includes two parts: Dose Escalation and Dose Expansion.

Figure 3.1: Study Schema: Dose Escalation



C = Cycle

CCI

[redacted]

3.2. Treatment Groups

In Dose Escalation, subjects will receive DS-1205c at varying doses based on their assigned cohort (see Table 3.1). In Dose Expansion, all subjects will receive the RDE dose as a single cohort.

3.2.1. Dose Escalation

3.2.1.1. Cycle 0 (Monotherapy, 7 Days)

To minimize the possibility of developing tumor flare with discontinuation of EGFR TKI, subjects who fulfill eligibility criteria will be instructed to continue their current EGFR TKI (gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib) during screening. The last dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib must be taken 1 day before breakfast in clinic on Cycle 0, Day 1, as depicted in Figure 3.1 above. This schedule provides an 8-day window between the last dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib, and the first dose of gefitinib.

Once eligibility is confirmed, subjects will be assigned by the Sponsor to receive DS-1205c at a specific dose level (Table 3.1). This will be either the current escalation dose (as determined by an algorithm described in detail in Section 3.2.1.2 below) or a previously assigned lower dose (ie, cohort backfilling).

Table 3.1: Dose Escalation Provisional Cohorts and Provisional Dosages

Cohort[a]	Cycle 0 Monotherapy (7-day cycle)	Cycle 1 and Beyond Combination Therapy (21-day cycles)	
	DS-1205c Dosage[b]	DS-1205c Dosage[b]	Gefitinib Dosage[c]
1	200 mg BID	200 mg BID	250 mg QD
2	400 mg BID	400 mg BID	250 mg QD
3	600 mg BID	600 mg BID	250 mg QD
4	800 mg BID	800 mg BID	250 mg QD

BID = twice daily; mg = milligrams; QD = once daily

a. The second subject in each cohort should start dosing at least 24 hours after the initial dosing of the first subject. The cohort numbers in this table do not denote actual order of dose transition on the trial.
b. Administer with a meal, with 240 mL of water. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS-1205c should be taken immediately after meal completion. Doses of DS-1205c should be taken approximately 12 hours apart.
c. Co-administer with morning dose of DS-1205c.

Subjects will report to the clinic on Day 1 before Cycle 0 to obtain ECGs at specified time points outlined in the Schedule of Events, Dose Escalation (Cycle 0) (see Table 6.1). These time points will be time matched to ECGs obtained on Cycle 0, Day 1.

Beginning with Cycle 0, Day 1, subjects will receive DS-1205c BID for 7 days. DS-1205c should be taken with a meal. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS-1205c should be taken immediately after meal completion. Time-matched ECGs will be obtained and blood samples for PK will be collected at specified time points (Table 6.1). Additional safety,

PK, and ECG assessments will be performed/obtained on specific days and time points over the 7-day run-in period (Section 6.1.2).

3.2.1.2. Cycle 1 and Beyond (Combination Therapy)

In Cycle 1 and beyond, DS-1205c will be taken BID in combination with 250 mg QD of gefitinib in 21-day cycles, as outlined in detail in the Schedule of Events, Dose Escalation, (Cycle 1 and Beyond) (Table 6.2).

Dose escalation of DS-1205c to determine the RDE will be guided by the modified Continuous Reassessment Method (mCRM) using a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle (Section 11.11). The logistic regression model for the dose-response (DLT rate) relationships will include 2 parameters: the intercept and slope. The DLT-evaluation period is defined as the 7 days of Cycle 0 plus the 21 days of Cycle 1 (28 days total). A DLT-evaluable subject is defined as a subject who has received DS-1205c and either has completed minimum safety evaluation requirements over the DLT-evaluation period or has experienced a DLT during the DLT-evaluation period. After at least 3 DLT-evaluable subjects of each cohort complete DLT evaluation, posterior distributions of DLT rate will be derived for all dose levels based on the BLRM using DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The EWOC principle requires that the mCRM-recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval with the overdose control constraint for excessive or unacceptable toxicity.

As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 DLT-evaluable subjects in the cohort experience DLT before the enrollment of the third subject. Enrollment of subjects to a new higher-dose cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed DLT evaluation nor experienced DLT will not be included in a BLRM update. In the event when subjects in the previous cohort experience DLTs after enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses. Subjects already receiving treatment will continue treatment at their assigned dose level or per dosing modification guidelines outlined in Section 5.4.

Subjects can be backfilled (added) to lower doses previously proven to be safe at any point during Dose Escalation. Lower or intermediate dose levels may also be considered based on review of available safety, tolerability, and PK data in this and other studies with the investigational agent. There will be no intrasubject dose escalation.

Any dose cohort may be expanded to include additional subjects for further evaluation of safety or PK parameters as required. The dose level for next cohort will be chosen by the Sponsor as outlined in Section 11.11.3 based on the dose recommendation by the mCRM, clinical assessment of TEAEs, toxicity profiles, efficacy, PK, and PD information observed thus far.

The number of treatment cycles is not fixed. Subjects may continue study treatment until PD, unacceptable toxicity, withdrawal of consent, or other reasons detailed in Section 5.6.1.

3.2.1.3. Dose-Limiting Toxicities (DLT)

A DLT is defined as any TEAE not attributable to disease or disease-related processes or to concomitant medications or procedures that occurs during the DLT-evaluation period (Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation) and is Grade 3 or above, according to NCI-CTCAE version 5.0, with the exceptions as defined below.

For hematological toxicities, a DLT is defined as follows:

Hematologic Dose-Limiting Toxicities (DLT) NCI-CTCAE version 5.0		
Hematological toxicity	**NCI-CTCAE Grade**	**CTCAE version 5.0 Definition**
Neutrophil count decreased	4 (Lasting > 7 days or neutrophil count decreased that requires supportive therapy with myeloid growth factors)	< 500/mm^3; < 0.5 × 10^9 /L
Febrile neutropenia	≥ 3	Grade 3: ANC < 1000/mm^3 with a single temperature of > 38.3°C or a sustained temperature of ≥38°C for more than one hour Grade4: Life-threatening consequences; urgent intervention indicated
Anemia	4	Life-threatening consequences; urgent intervention indicated rade4:
Platelet count decreased	≥ 3 Lasting > 7 days or with clinically significant hemorrhage	Grade 3: < 50,000 – 25,000/mm^3; < 50.0 – 25.0 × 10^9 /L Grade 4: < 25,000/mm^3; < 25.0 × 10^9 /L
Lymphocyte count decreased	4 Lasting ≥ 14 days	< 200/mm^3; < 0.2 × 10^9 /L
Any	5	Death

For hepatic organ toxicities, a DLT is defined as follows:

Hepatic Dose-Limiting Toxicities (DLT) NCI-CTCAE version 5.0		
Hepatic Organ Toxicity	**NCI-CTCAE Grade**	**CTCAE version 5.0 Definition**
Serum aspartate aminotransferase (AST) increase	4	> 20.0 × the upper limit normal (ULN) if baseline was normal; > 20.0 × baseline if baseline was abnormal
Serum alanine aminotransferase (ALT) increase	4	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal
AST or ALT increased	3 Lasting >5 days	> 5.0 – 20.0 × ULN if baseline was normal; > 5.0 – 20.0 × baseline if baseline was abnormal
ALT or AST increased ≥ 3.0 × ULN with simultaneous TBL increased ≥ 2.0 × ULN	Not applicable	Not applicable
Any	5	Death

For pulmonary toxicities, a DLT is defined as any of the following:

Pulmonary Dose-Limiting Toxicities (DLT) NCI-CTCAE version 5.0		
Pulmonary Toxicity	**NCI-CTCAE Grade**	**CTCAE version 5.0 Definition**
Confirmed interstitial lung disease (ILD)	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL)
	3	Severe symptoms; limiting self care ADL; oxygen indicated
	4	Life-threatening respiratory compromise; urgent intervention indicated (eg., tracheotomy or intubation)
	5	Death
Any other pulmonary toxicity	≥ 3	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of

		existing hospitalization indicated; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5:Death

For non-hematological, non-hepatic, or non-pulmonary organ toxicities (ie, any other Grade ≥3 non-hematologic, non-hepatic, non-pulmonary toxicities including Grade 5 events), a DLT is defined as any of the following:

Dose-Limiting Toxicities (Non-Hematologic, Non-Hepatic, Non-Pulmonary Toxicities)		
DLT	**NCI-CTCAE Grade**	**CTCAE version 5.0 Definition**
Symptomatic heart failure	2	Symptoms with moderate activity or exertion
	3	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms
Left ventricular ejection fraction (LVEF)	3	Resting ejection fraction (EF) 39 – 20%; ≥20% drop from baseline
Endocrine toxicities	≥ 3 Which do not resolve in ≤ 14 days	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated

The following TEAEs are considered DLTs
Thrombocytopenia requiring transfusion. Anemia requiring transfusion Inability to complete at least 75% of the prescribed doses (ie, at least 42 doses of DS-1205c and 16 doses of gefitinib) in the 7 days of Cycle 0 and the 21 days of Cycle 1 as a result of Grade ≥ 2 AE not attributed to disease.

The following TEAEs are NOT considered DLTs:

The following TEAEs are NOT considered Dose Limiting Toxicities		
TEAE	**NCI-CTCAE Grade**	**CTCAE version 5.0 Definition**
Fatigue	3 Lasting ≤ 7 days	Fatigue not relieved by rest, limiting self care ADL
Nausea	3 That resolves to ≤ grade 2 in 48 hours	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Vomiting	3 That resolves to ≤ grade 2 in 48 hours	Tube feeding, TPN, or hospitalization indicated
Diarrhea	3 That resolves to ≤ grade 2 in 48 hours	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
Anorexia	3 That resolves to ≤ grade 2 in 48 hours	Associated with significant weight loss or malnutrition (eg., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated
Isolated laboratory findings not associated with signs or symptoms, including • Grade 3 or 4 serum ALP increased, hyperuricemia, serum amylase increased, lipase increased, or grade 3 hyponatremia, lasting < 72 hours		
Lymphocyte count	3	< 500 – 200/mm^3; < 0.5 – 0.2 × 10^9 /L
Subjects missing more than 25% of scheduled doses in Cycle 0 and Cycle 1 for reasons not related to AEs (eg, noncompliance) will not be evaluable for DLT.		

Management of study drug-related AEs will be as per treating physician discretion and institutional guidelines. See Section 5.5 for information regarding the use of concomitant medications.

3.2.1.3.1. TEAEs During Cycle 0

In the event of a TEAE within Cycle 0 that may delay the start of Cycle 1, Day 1, Investigators should contact the Sponsor medical monitor or designee for guidance. Investigators should refer to Section 5.4 for information on interruptions of dose.

3.2.1.4. Safety Review Meetings

Investigators will communicate with the Sponsor any incidence of DLT on a real-time basis.

Safety review meetings (SRMs) will include at least the Investigators and the Sponsor's medical monitor.

During Dose Escalation, SRMs will occur as needed to make determinations about enrollment and dose escalation according to the DLT-dependent mCRM, and to determine the RDE.

During Dose Expansion, SRMs will occur as needed to assess safety and tolerability of the selected RDE.

3.2.1.5. Stopping Rule for Recommended Dose for Expansion Determination

Dose Escalation will be stopped if any of the following occur:

a. at least 6 evaluable subjects have been enrolled at the RDE level with at least 18 evaluable subjects, in total, enrolled in Dose Escalation, OR
b. at least 9 evaluable subjects have been enrolled at a particular dose level, the model recommends continuing at the same dose level, and the posterior probability of the DLT rate falling within the target DLT interval is $\geq 50\%$. The target DLT interval is defined as $16\% < \text{DLT rate} \leq 33\%$ (Section 11.11.3), OR
c. the initial dose level is too toxic.

3.2.1.6. Determination of Recommended Dose for Expansion

Once the dose escalation stopping criteria are met, the RDE determination will be guided by mCRM using a BLRM with EWOC (Section 3.2.1.2). The RDE will be decided based on an overall assessment of available safety data from Cycle 1 and beyond, and all available PK, biomarker, and tumor response data.

3.2.2. CCI [redacted]

[redacted]

3.2.2.1. Stopping Rule for Other Consideration(s)

The Sponsor has the right to terminate the study at any time, and study termination may also be requested by (a) competent authority(-ies).

3.3. Duration of Subject Participation

The Eligibility Screening period is up to 22 days for Dose Escalation Part and 30 days for Dose Expansion Part. Each cycle of treatment (except for Cycle 0 in Dose Escalation) is 21 days.

The number of treatment cycles is not fixed in this study. Subjects may continue study treatment until PD, unacceptable toxicity, withdrawal of consent, or other reasons detailed in Section 5.6.1.

3.4. Duration of Study

This study is expected to last approximately 3 years from the time the first subject is enrolled to the time the last subject is off the study. The end of the study is defined as the last subject visit or contact, including telephone contacts, for collection of any study-related data.

Dose Escalation

- Enrollment is planned to occur over approximately 12 months.
- Treatment and follow-up will be completed when all subjects have either discontinued study treatment or completed last study visit.

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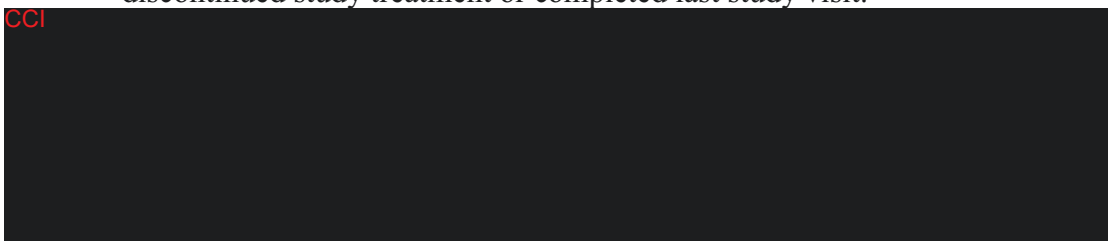


4. STUDY POPULATION

Subjects must satisfy all of the following inclusion and exclusion criteria to participate in either Dose Escalation or Dose Expansion:

4.1. Inclusion Criteria

1. Male or female subjects aged 20 years and older.
2. Has histologically or cytologically documented adenocarcinoma NSCLC.
3. Has locally advanced or metastatic NSCLC, not amenable to curative surgery or radiation.
4. Has acquired resistance to EGFR TKI according to the Jackman criteria.[36]
    a. Historical confirmation that the tumor harbors an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q), OR
    b. Has experienced clinical benefit from an EGFR TKI, followed by systemic progression of disease (RECIST version 1.1 or World Health Organization [WHO]) while on continuous treatment with an EGFR TKI.
5. Is currently receiving and able to interrupt gefitinib or discontinue erlotinib, afatinib, dacomitinib, or osimertinib.
6. Has been receiving gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib for at least 6 weeks with well-controlled related toxicities less than Grade 3 in severity at the time of screening period. Subjects who have been receiving gefitinib must be taking gefitinib at a dose of 250 mg/day.
7. Has radiological documentation of disease progression while receiving continuous treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.
8. Has at least one measurable lesion per RECIST version 1.1.
9. Is willing to provide archival tumor tissue from a biopsy performed after progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib OR has at least one lesion, not previously irradiated, amenable to core biopsy and is willing to undergo screening tumor biopsy.
10. Demonstrates absence of EGFR T790M mutation in tumor tissue since progression during gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib treatment.
11. Has ECOG PS of 0 or 1, with no deterioration over the previous 2 weeks. A table of the ECOG PS scale can be found in Appendix Section 17.4.
12. Has adequate bone marrow reserve and organ function, defined as:
    a. Platelet count $\geq 100 \times 10^9$/L
    b. Hemoglobin (Hb) ≥ 9.0 g/dL
    c. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

d. Prothrombin time and activated partial thromboplastin time (aPTT) ≤ 1.5 × the upper limit normal (ULN), except for patients on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have prothrombin time-International Normalized Ratio (PT-INR) within therapeutic range as deemed appropriate by the Investigator.
e. Serum creatinine ≤ 1.5 × ULN, or creatinine clearance ≥ 50 mL/min as calculated using the Cockcroft-Gault equation (Section 17.1); confirmation of creatinine clearance is only required when creatinine is > 1.5 × ULN.
f. AST/ALT ≤ 3.0 × ULN (if liver metastases are present, ≤ 5.0 × ULN).
g. Total bilirubin ≤ 1.5 × ULN if no liver metastases or < 3.0 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases.
h. CK < 1.5 × ULN.
i. Lipase < 2 × ULN.

13. Has adequate treatment washout period before first dose of study drug, defined as:

    a. QTc prolonging medications ≥ 10 days (Section 17.6)
    b. CYP3A4 strong inducers ≥ 10 days (Section 17.6)
    c. Proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole) ≥ 5 days

14. Female subjects of reproductive/childbearing potential with a male sexual partner must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 3 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective birth control include:

    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery). *
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery). *
    c. Intrauterine device (IUD).
    d. Intrauterine hormone-releasing system (IUS).
    e. Bilateral tubal occlusion.
    f. Vasectomized partner.
    g. Complete sexual abstinence.

    Non-child-bearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥ 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] > 40 mIU/mL and estradiol < 40 pg/mL [< 147 pmol/L] is confirmatory).

    Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined above for women of child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-

menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Female subjects must not retrieve ova or donate from the time of screening and throughout the study treatment period, and for ≥ 3 months after the final dose of study drug.

* Only oral agent are approved in Japan.

15. A male subject with a sexual partner who is a woman of child-bearing potential must be willing and able to use a highly effective contraceptive method for the entire study treatment period and for ≥ 3 months after the final dose of study drug.
    a. Acceptable forms of contraception include condoms and highly effective contraception used by the usual female partner (see above for forms of highly effective contraception).
    b. Male subjects must not freeze or donate sperm starting at screening and throughout the study period, and ≥ 3 months after the final dose of study drug.
16. Subjects must be fully informed about their illness and investigational nature of the protocol (including foreseeable risks and possible side effects) and sign and date an Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)-approved Informed Consent Form (ICF) before performance of any study-specific procedures or tests.
17. Is willing and able to complete a daily study medication diary.

4.2. Exclusion Criteria

1. Has any evidence of small cell histology, or combined small cell and non-small cell histology, in original tumor biopsy or in screening biopsy performed since progression.
2. Has previously documented evidence of anaplastic lymphoma kinase (ALK) fusion, ROS proto-oncogene 1 (ROS1) fusion, BRAF V600E mutation, rearranged during transfection (RET) rearrangement, human epidermal growth factor receptor 2 (HER2) mutation, or MET exon 14 skipping mutation. No new testing for these genomic alterations is required for Screening.
3. Has received treatment with any of the following:
    a. Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), within 14 days of the first dose of study treatment
    b. Immune checkpoint inhibitor therapy within 30 days of first dose of DS-1205c.
    c. Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment

   d. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks, or palliative radiation therapy within 2 weeks of the first dose of study drug treatment.

4. Has history of other active malignancy within 3 years prior to enrollment, except:
   a. Adequately treated non-melanoma skin cancer OR
   b. Superficial bladder tumors (Tumor stage “a” [Ta], Tumor stage “is” [Tis], Tumor stage “1” [T1]) OR
   c. Curatively treated in situ disease OR
   d. Low-risk non-metastatic prostate cancer (with Gleason score < 7 on antiandrogen therapy)
5. Clinically significant malabsorption syndrome or other gastrointestinal disease (eg, persistent diarrhea, or known sub-acute bowel obstruction ≥ NCI-CTCAE v5.0 Grade 2, despite medical management) that would impact drug absorption.
6. Presence of retinal disease in the eye that is not due to neovascular age-related macular degeneration (nAMD; eg, significant diabetic retinopathy, glaucomatous retinal atrophy, retinal detachment).
7. Has spinal cord compression or clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy).
8. Has history of myocardial infarction within the past 6 months.
9. Has symptomatic congestive heart failure (New York Heart Association [NYHA] Classes II IV), unstable angina, or cardiac arrhythmia requiring antiarrhythmic treatment.
10. Has LVEF < 45% by either ECHO or MUGA.
11. Has any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval > 250 ms.
12. Has a mean QTcF prolongation to > 470 ms for females and > 450 ms for males in three successive Screening measurements.
13. Unable or unwilling to discontinue concomitant drug that may influence gefitinib or DS-1205c metabolism.
14. Unable or unwilling to discontinue concomitant use of drugs that are known to prolong the QT interval. (See Section 17.6).

15. Has any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives.
16. Has a history of (non-infectious) ILD/pneumonitis that required corticosteroid treatment, has current ILD/pneumonitis, or has suspected ILD/pneumonitis which cannot be ruled out by imaging at screening.
17. Has history of pancreatitis within the past 6 months.
18. Has any evidence of severe or uncontrolled systemic diseases including uncontrolled hypertension, active bleeding diatheses or active infection (including hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]), psychiatric illness/social situations, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
19. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days before enrollment.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequence(s)

This study is an open-label, non-randomized study. DS-1205c will be administered orally at a starting dose level of 200 mg BID in combination with a fixed dose of 250 mg gefitinib administered orally QD in cycles of 21 days, except for Cycle 0 of Dose Escalation, where DS-1205c will be administered BID as monotherapy. Additional dose levels of DS-1205c may be tested based on the emerging data from Dose Escalation and the proposed lower doses.

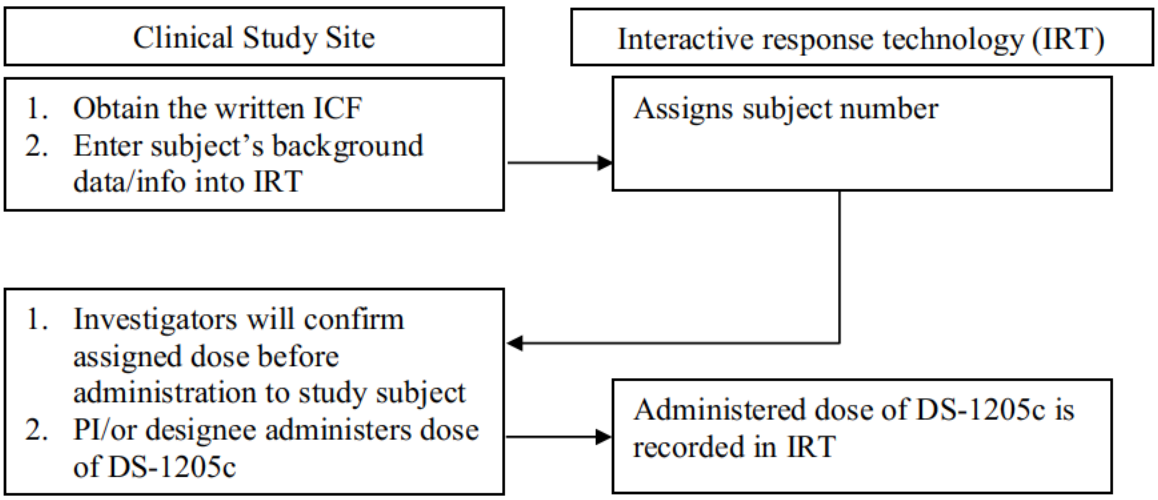
In Dose Escalation, each dose cohort is planned to include at least three subjects. Subjects are assigned to dose cohorts by the Sponsor as detailed in Section 3.2.1.2 above. For additional safety, the second subject in each dose cohort should start dosing at least 24 hours after the initial dosing of the first subject.

CCI [redacted]

5.1.2. Enrollment

Subject enrollment is conducted at central interactive response technology (IRT). Enrollment process is described in Figure 5.1.

Figure 5.1: Subject Enrollment Process



The investigators will obtain the written ICF, and enter subject's background data/info into IRT. Upon the Investigator's determination of all inclusion and exclusion criteria having been satisfied, the subject's enrollment data will be entered into the IRT. The date of enrollment is defined as the date that the subject is confirmed and registered as eligible in the IRT. The date of screen failure is defined as the date that the subject is confirmed ineligible by the Investigator.

5.2. Study Drug(s)

5.2.1. Description

The Investigator must ensure that the study drugs will be used only in accordance with the protocol.

DS-1205c is supplied as 200 mg capsules white opaque with red lines. Each DS-1205c 200 mg capsule contains a 200 mg equivalent of DS-1205a (free form).

5.2.2. Labeling and Packaging

DS-1205c will be packaged in high-density polyethylene (HDPE) bottles (32 capsules/bottle) labeled with the study drug name, strength, batch number, storage information, and Sponsor information.

The study site will dispense the take-home medications and will instruct the subjects on their use.

Local regulations concerning use of study drugs will be followed.

5.2.3. Preparation

All study drugs will be supplied as capsules or tablets that need no further preparation at the study sites. Procedures for proper handling and disposal of anticancer drugs should be followed in accordance with the standard operating procedures (SOPs) of the study site.

5.2.4. Administration

DS-1205c

- Administer with a meal, with 240 mL of water. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS-1205c should be taken immediately after meal completion. DS-1205c is administered as BID doses to be taken approximately 12 hours apart.
- Doses missed by more than 6 hours should be skipped, and any missed dose should be recorded by the subject in the Study Medication Diary.

When DS-1205c is not be administered as specified in the protocol, such as overdose and missed doses, the Investigator will promptly understand the situation and take the necessary measures.

In the event of overdose, the subject should immediately be inspected for any symptoms or signs, and the necessary examinations will be performed, including laboratory tests and 12-lead ECG. At the same time, the event should be reported to the Sponsor. The Sponsor will give instructions as to the dose of DS-1205c on and after the following day.

Gefitinib

- Co-administer with the morning dose of DS-1205c.
- Doses missed by more than 12 hours should be skipped, and any missed dose should be recorded by the subject in the Study Medication Diary.

If a subject experiences vomiting after a dose of DS-1205c during Cycle 0, the subject may receive antiemetic treatment. If a subject vomits any dose of DS-1205c or gefitinib, that dose should not be replaced.

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the storage conditions listed below:

DS-1205c

- Capsules should be stored at up to 25°C. Excursions permitted up to 30°C in HDPE bottles.

If storage conditions go out of specified requirement, contact the Study Contract Research Organization (CRO).

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be signed, and the original form will be retained at the site. In addition, the Investigator or designee shall contact Sponsor or designee as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drug. The record must be kept current and should contain the following:

- Dates and quantities of drug received,
- Subject's identification number, subject's initials, or supply number (as applicable),
- The date and quantity of study drug dispensed and remaining (if from individual subject drug units),
- The initials of the dispenser.
- Manufacturing number or symbol
- Expiration Date

The study monitor will review study drug accountability records during the study and/or at the end of the study. All study drug inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for maintaining the accountability of all used and unused study supplies at the site.

At the end of the study, or as directed, all unused, used, and/or partially used study drug will be destroyed at the site per institutional policy (and documented). As applicable, the study site must file a copy of the appropriate institutional destruction policy (and documents) and/or Sponsor return documentation in its Investigator site file and provide a copy to the Sponsor.

If the site's institutional policy does not allow for destruction on site, study drug will be returned to a designee as instructed by the Sponsor. The return of study drug must be documented and the documentation included in the shipment. Study drugs will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned.

At the end of the study, a final study drug reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor.

5.3. Treatment Compliance

The following measures will be employed to ensure treatment compliance during dosing at the clinical site:

- When study medication is administered in the clinic, it should be administered to subjects under the supervision of clinical study personnel at the site.
- DS-1205c and gefitinib may be dispensed in amounts exceeding the minimum amount required for the period of time until the next visit. Subjects will be instructed to return all unused DS-1205c and gefitinib at the next visit. Alternatively, to ensure compliance, the site personnel may choose to dispense only the adequate amount of study drug required until the next scheduled visit. Study medication dispensing should occur as per site's standard operating procedure (SOP) with approval from the Sponsor or CRO. Compliance with the study drug regimen will be determined by counting unused capsules/tablets.
- A Study Medication Diary will be provided to patients at the start of the study in order to document the study drug doses taken and the associated meals. The Investigator or designee will review the diary and document treatment compliance for each subject at each visit. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

5.4. Dose Interruptions and Reductions

Following the DLT evaluation period (Section 3.2.1.3), the Investigator will evaluate which toxicities are attributed to the study drug and adjust the administration schedule of the drug.Table 5.1 outlines schedule modifications for specific toxicities. Doses may also be interrupted for other toxicities per Investigator discretion, and supportive medication may be administered in accordance with local practice guidelines. All interruptions must be recorded on the drug administration electronic Case Report Form (eCRF).

In the event of a dose delay occurring prior to completion of a PK blood sampling in the study, Investigators should contact Sponsor medical monitor or designee for guidance regarding scheduling of these procedures.

5.4.1. Dose Interruptions

During the DLT evaluation period, the administration of study drugs may be interrupted due to DLTs for up to 21 days according to the rules listed in Table 5.1 below. When a DLT triggered interruption is required, both DS-1205c and gefitinib should be held. If a subject requires a dosing delay longer than 21 days, the subject will be withdrawn from the study.

For non-DLT TEAEs Grade 3 and above, study medications will be withheld for up to 3 weeks until improvement of the TEAE to Grade 2 or below. Study medications may be resumed after discussion and agreement between the Investigator and Sponsor. If the dosing interruption exceeds 21 days, the subject will be withdrawn from the study.

Table 5.1: Dose Interruption and Dose Resumption Criteria

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
General disorders and administration site conditions		
Fatigue/ Generalized muscle weakness	Grade 3 (Fatigue not relieved by rest, limiting self care ADL)	Delay study medications until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, resume study medications. • If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. • If not resolved in > 21 days, discontinue subject from treatment.
Blood and lymphatic system disorders		
Neutrophil count decreased	Grade 3 (< 1000-500/mm^3; < 1.0 - 0.5 × 10^9/L) Grade 4 (< 500/mm^3; < 0.5 × 10^9/L)	Delay study medications until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, resume study medications. • If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. • If not resolved in > 21 days, discontinue subject from treatment.
Febrile neutropenia	Grade 3 (ANC < 1000/mm^3, with a single temperature > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour) Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay study medications until neutrophil count decreased resolved to ≤ Grade 2. Study medications may be resumed after discussion and agreement between the Investigator and Sponsor.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
Lymphocyte count decreased	Grade 3 (<500-200/mm^3; <0.5-0.2 × 10^9/L): Grade 4 (< 200/mm^3; < 0.2 × 10^9/L)	Delay study medications until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, resume study medications. • If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. • If not resolved in >21 days, discontinue subject from treatment.
Anemia	Grade 3 (Hb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated) Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay study medications until resolved to ≤ Grade 2, then • If resolved in ≤ 7 days, resume study medications. • If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. • If not resolved in > 21 days, discontinue subject from treatment.
Platelet count decreased	Grade 3 (< 50,000 - 25,000/mm^3; < 50 - 25 × 10^9/L) Grade 4 (< 25,000/mm^3; < 25.0 × 10^9/L)	Delay study medications until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, resume study medications. • If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. • If not resolved in > 21 days, discontinue subject from treatment. Consider transfusion per institutional guidelines.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
Cardiac Disorders		
Heart Failure	Grade 2 (Symptoms with moderate activity or exertion) Grade 3 (Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms) Grade 4 (Life-threatening consequences; urgent intervention indicated [eg, continuous IV therapy or mechanical hemodynamic support])	Discontinue subject from study treatment. Cardiologist consult as necessary. Medical intervention as per institutional guidelines.
Ejection fraction (EF) decreased	Grade 3 (Resting EF 39 - 20%; ≥ 20% drop from baseline)	Delay study medications until resolved to ≤ Grade 2, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment. Repeat LVEF assessment within 3 weeks. Cardiologist consult as necessary.
	Grade 4 (Resting EF < 20 %)	Discontinue subject from study treatment. Cardiologist consult as necessary.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
Electrocardiogram QT corrected interval prolonged	Grade 3 (Average QTc ≥ 501 ms; QTc [ΔQTc] >60 ms change from-baseline)	Delay study medications until resolved to ≤ Grade 1 (Average QTc 450 - 480 ms). Determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If mean QTcF prolongation is attributed to study treatment(s), the Investigator should have a discussion with the Sponsor before resuming study medications.
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment. Cardiologist consult as necessary.
Respiratory, thoracic and mediastinal disorders		
Respiratory, thoracic and mediastinal disorders	Grade 2 (Symptomatic; medical intervention indicated; limiting instrumental ADL) Grade 3 (Severe symptoms; limiting self care ADL; oxygen indicated) Grade 4 (Life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheotomy or intubation])	If new or worsening pulmonary symptoms (eg, dyspnea, cough, low-grade fever) or radiological abnormality suggestive of interstitial lung disease (ILD) is observed, an interruption in study treatment dosing is recommended, and the Sponsor should be informed . If a subject is suspected or diagnosed as having ILD, the Investigator should consult with a pulmonologist as needed, and the subject should be treated accordingly. The results of the full diagnostic workup (eg, high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters, arterial blood gas (ABG), pulmonary function testing, diffusing capacity of the lungs for carbon monoxide [DLCO]) should be recorded within the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage Unscheduled imaging and laboratory results should be included in the eCRF.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
		If a non-inflammatory cause is confirmed, this should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. Study treatment will be permanently discontinued upon confirmation of drug-induced ILD or drug-induced pneumonitis.
Endocrine disorders	Grade 3 (Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL)	Delay dose until resolved to ≤ Grade 2, then: ● If resolved in ≤ 14 days, resume study medications. ● If resolved in > 14 days and ≤ 21 days, study treatment may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from study treatment.
Nervous system disorders	Grade 3 (Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL) Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay study medications and monitor at least twice a week until resolved to ≤ Grade 2, then: ● If resolved in ≤7 days, resume study medications. ● If resolved in >7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment. Unscheduled imaging of the brain or spinal cord may also be conducted to evaluate subjects.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
Eye disorders	Grade 3 (Severe or medically significant but not immediately sight-threatening; decrease in visual acuity [best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200])	Delay dose until resolved to ≤ Grade 2, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment. Ophthalmologist consult as necessary.
	Grade 4 (Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye)	Discontinue subject from study treatment. Ophthalmologist consult as necessary.
	Corneal ulceration, any Grade	Discontinue subject from study treatment. Ophthalmologist consult as necessary.
Renal and urinary disorders		
Creatinine increased	Grade 3 (> 3.0 × baseline; > 3.0 - 6.0 × ULN)	Delay dose until resolved to ≤ Grade 2 (>1.5 - 3.0 × ULN; >1.5 - 3.0 × baseline), then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. If not resolved in > 21 days, discontinue subject from treatment.
	Grade 4 (> 6.0 × ULN)	Discontinue subject from study treatment.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
Hepatobilliary disorders		
AST or ALT increased	Grade 2 (> 3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	If simultaneous TBL increased ≥ 2.0 × ULN, then see "AST or ALT increased with simultaneous TBL increased" below. Otherwise: ● Continue study medications. ● Monitor AST/ALT 48 to 72 hours later, and continue regular monitoring until resolution.
	Grade 3 (> 5.0 - 20.0 × ULN if baseline was normal; > 5.0 - 20.0 × baseline if baseline was abnormal)	If simultaneous TBL increased ≥ 2.0 × ULN, then see "AST or ALT increased with simultaneous TBL increased" below. Otherwise: Delay study medications until resolved to ≤ Grade 2. Monitor AST/ALT 48 to 72 hours later, and continue regular monitoring until resolved to ≤Grade 2. ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in >21 days, discontinue subject from treatment.
	Grade 4 (> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	If simultaneous TBL increased ≥ 2.0 × ULN, then see "AST or ALT increased with simultaneous TBL increased" below. Otherwise: Discontinue subject from study treatment. Monitor AST/ALT 48 to 72 hours later, and continue regular monitoring until resolved to ≤Grade 2. Gastroenterologist or hepatologist consult as necessary.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
AST or ALT ≥ 3.0 × ULN with simultaneous TBL ≥ 2.0 × ULN		Delay study medication until drug-induced liver injury can be ruled out. The Investigator should consult with a gastroenterologist or hepatologist as needed, and the subject should be treated accordingly. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as viral or autoimmune hepatitis, alcoholic liver injury, biliary tract disorders, or hemodynamic abnormalities. Results from diagnostic workup (including, for example: INR, direct bilirubin, serologic tests for hepatitis A, B, and C; alcohol use, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scan, concomitant medication use, immunoglobulin levels, ECHO) should be recorded within the eCRF. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor.Study treatment will be permanently discontinued if drug-induced liver injury cannot be ruled out from diagnostic workup. Gastroenterologist or hepatologist consult as necessary.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
TBL increased	Grade 2 (> 1.5 – 3.0 × ULN if baseline was normal; >1.5 – 3.0 × baseline if baseline was abnormal)	Continue study medications.
	Grade 3 (> 3.0 – 10.0 × ULN if baseline was normal; >3.0 – 10.0 × baseline if baseline was abnormal),	Delay study medications until resolved to ≤ Grade 2, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment.
	Grade 4 (with or without liver metastases or Gilbert's syndrome) (> 10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment. Gastroenterologist or hepatologist consult as necessary.
Skin disorders		
Skin reactions	Grade 3 (Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL)	Delay study medications until resolved ≤ Grade 2, and consider treatment per local practice/guidelines, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● Discontinue study drugs if event has not resolved in > 21 days.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	**Schedule modification for DS-1205c and gefitinib**
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from study treatment.
Gastrointestinal disorders		
Nausea	Grade 3 (Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated)	Delay study medications until resolved ≤ Grade 2, and consider anti-nausea treatment per local practice/guidelines, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment.
Diarrhea/Colitis	Grade 3 (Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL)	Delay study medications until resolved ≤ Grade 2, and consider anti-diarrheal treatment per local practice/guidelines, then: ● If resolved in ≤ 7 days, resume study medications. ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from study treatment.

Table 5.1: Dose Interruption and Dose Resumption Criteria (Continued)

	Worst toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified) by Definition	Schedule modification for DS-1205c and gefitinib
Other laboratory AEs	Grade 3	Delay study medications until resolved to ≤ Grade 2, then: ● If resolved in ≤ 7 days, resume study medications ● If resolved in > 7 days and ≤ 21 days, study medications may be resumed after discussion and agreement between the Investigator and Sponsor. ● If not resolved in > 21 days, discontinue subject from treatment.
	Grade 4	Discontinue subject from study treatment

ABG = arterial blood gas; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE: Common Toxicity Criteria for Adverse Events; DLCO = diffusing capacity of the lungs for carbon monoxide; ECHO = echocardiogram; eCRF = electronic Case Report Form; g/dL = grams per deciliter; Hb = hemoglobin; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; L = liter; LVEF = left ventricular ejection fraction; ms = milliseconds; NCI = National Cancer Institute; QTcF = corrected QT using Fridericia's formula; TBL = total bilirubin; ULN = upper limit of normal.
A There will be no dose interruptions for Grade 1 to Grade 3 lymphopenia.

Possible exceptions to the above may be allowed on a case-by-case basis after discussion and agreement between Investigator and Sponsor. The agreement must be documented.

5.4.2. Dose Reductions

Dose reductions of DS-1205c and gefitinib may be permitted following a discussion between the Investigator and the Sponsor. The final decision should be documented and filed at the site.

No dose reductions of gefitinib will be allowed for DLT evaluation period of dose escalation part.

5.5. Prior and Concomitant Medications, Treatments, and Procedures

5.5.1. Prior Medication(s), Treatment(s), and Procedure(s)

All prior anticancer treatments or procedures (eg, surgery, radiation therapy, TKI therapy, chemotherapy, immune checkpoint inhibitor therapy) will be recorded. All medications taken by subjects within 22 days prior to the first dose of DS-1205c will be recorded as prior medications.

5.5.2. Concomitant Medication(s)

Concomitant medications, ie, medications used from the first dose of DS-1205c until 30 days after the last dose of study drug or the start of any new anticancer treatment, whichever comes first, will be recorded. All concomitant medications will be recorded on the eCRF.

Management of study drug-related AEs will be as per treating physician discretion and institutional guidelines.

Hematopoietic growth factors (HGFs) may be used for treatment based on the clinical judgment of the Investigator. HGFs (e.g. G-CSF.) should not be used prophylactically during the DLT evaluation period. Use of prophylactic HGFs may be considered after Cycle 1 following discussion with the Sponsor. (Treatment with HGFs for anemia associated with chemotherapy is not approved in Japan)

Bisphosphonates (eg, pamidronate or zolendronate) or denosumab for control of bone pain, treatment of bony metastases, or treatment of osteoporosis, may be used per clinical judgment of the Investigator and according to prescribing information and institutional guidelines.

5.5.3. Prohibited Medications

The following medications, treatments and procedures will be prohibited (with noted exceptions below) from enrollment until the End-of-Treatment (EOT) visit, in both Dose Escalation and Dose Expansion:

- Other anticancer therapy, including cytotoxic chemotherapy, targeted agents, immunotherapy, endocrine therapy, or TKIs (other than gefitinib)
- Other investigational therapeutic agents
- Radiotherapy (except for palliative radiation)
- Radiotherapy to the thorax
- Concomitant use of chronic systemic corticosteroids or other immunosuppressive medications (inhaled corticosteroids or intra-articular steroid injections are permitted in this study)
- The use of concomitant medications that prolong the QTc (See Section 17.6)
- Foods containing *Hypericum perforatum* (St. John's Wort)
- Foods or beverages containing grapefruit
- Use of gastric acid-reducing agents (eg, proton pump inhibitors or histamine 2 receptor antagonists)

  Use of antacids is allowed. Any antacid should be used ≥ 2 hours before or after DS-1205c dosing, and should be used ≥ 6 hours before or after gefitinib dosing

- Strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin). (See Section 17.6)
- Avoid strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, ritonavir, nefazodone, voriconazole) if possible. Medical judgment should be used when administering concomitant strong CYP3A4 inhibitors. (See Section 17.6)
- Avoid co-administration of UGT1A1 and UGT1A4 inhibitors (eg, valproic acid, probenecid) and inducers (eg, dexamethasone, phenobarbital, rifampicin) if possible. Medical judgment should be used when administering concomitant inhibitors or inducers of UGT1A1 and UGT1A4
- Avoid co-administration of BCRP substrates (eg, rosuvastatin) if possible. Medical judgment should be used when administering concomitant substrates of BCRP
- It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low-density lipoprotein (LDL) cholesterol levels is advised. If the subject experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, CK level should be checked, and any appropriate further management should be taken
- Avoid co-administration of P-gp substrates (eg, digoxin) if possible. Medical judgment should be used when administering concomitant substrates of P-gp

Subjects who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE Grade ≤ 2) while receiving treatment until at least one week after symptoms have resolved. If a subject has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥ 3) ocular events they must discontinue wearing their contact lenses until at least one week after treatment is permanently discontinued. Subjects must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study ≥ 1 week after permanent discontinuation of study treatment. Subject should consult the clinic promptly if they have any concerns.

Subjects taking warfarin should be monitored regularly for changes in prothrombin time or PT-INR.

5.6. Subject Withdrawal/Discontinuation

5.6.1. Reasons for Withdrawal/Discontinuation

Subjects may be withdrawn from the study for the following reasons:

- PD per criteria set forth in RECIST version 1.1 (Section 17.2)

- Clinical progression (definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for PD according to RECIST version 1.1)
- AE
- Withdrawal of consent by subject
- Investigator discretion
- Death
- Pregnancy
- Study terminated by Sponsor
- Lost to follow-up
- Other, specify

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized. All subjects who are withdrawn from study treatment should complete protocol-specified withdrawal procedures (Section 5.6.2).

Record the reason for treatment discontinuation for any subject who discontinues study treatment for any reason.

Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.6.2. Withdrawal Procedures

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

Protocol-specified withdrawal procedures will involve an EOT visit and a follow-up phone call 30 days after the last administration of DS-1205c and gefitinib. If a subject begins another anticancer therapy before the end of the 30-day period, all of the EOT assessments should be completed prior to commencing the new therapy(-ies). Protocol-specified withdrawal procedures are the same as those to be performed at the EOT visit (Section 6.1.3.8 or Section 6.2.2.9).

If the subject is withdrawn due to reasons other than death, withdrawal of consent, loss to follow-up, or study closure, and received study treatment, they should be followed for survival and subsequent anticancer therapy (Section 6.1.3.10 and Section 6.2.2.11).

5.6.3. Subject Re-Screening Procedures

The study will allow 1 re-screening for any subject who failed to meet eligibility criteria upon initial screening or whose screening window has elapsed. The Investigator will consult with the Sponsor before making the re-screen decision. The subject identification (SID) number must remain the same at the time of re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be

recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for re-screening subjects.

6. STUDY PROCEDURES

6.1. Dose Escalation

In consideration of the subject's safety, the subjects will be hospitalized from Day 2 (Cycle 0, Day 2) to Day 30 (Cycle 2, Day 2) in Dose Escalation to allow for careful safety monitoring. However, temporary discharge or leave may be permitted at the Investigator's discretion after Day 15 (Cycle 1, Day 8), taking the subject's safety into consideration. Investigator should examine the subject carefully before granting temporary discharge or leave, and the study site should train the subject about an emergency contact.

6.1.1. Screening (Dose Escalation)

6.1.1.1. Tissue Requirement (Dose Escalation)

All subjects will be required to provide tumor tissue from a biopsy, collected within 6 months of the date of consent, performed since progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.

To meet entry criteria, subjects are required to demonstrate an absence of EGFR T790M mutation prior to study entry, assessed in tumor tissue using either cobas® EGFR Mutation Test v2 or gene panel testing (FoundationOne CDx™ or OncoGuide™ NCC Oncopanel System) performed locally at a College of American Pathologists (CAP) or an International Organization for Standardization (ISO)15189 certified laboratory.

The following procedures should be conducted:

- Have the subject sign the appropriate ICF before any study-related procedures assessments are performed
- Perform a tumor biopsy OR
- Request archive tumor tissue sample (if collected within 6 months of the date of consent) and confirm that it meets the tumor tissue requirements (eg, adequate amount for local and central analyses) for the study as noted in the Laboratory Manual

  If archival tissue does not meet requirements a new core tumor biopsy must be obtained
- Test the EGFR mutation in tumor tissue using either cobas® EGFR Mutation Test v2 or gene panel testing (FoundationOne CDx™ or OncoGuide™ NCC Oncopanel System) at local CAP or ISO15189-certified laboratory
- Send the sample(s) to be tested using cobas® EGFR Mutation Test v2 at central laboratory and for exploratory biomarker analysis. (The results obtained from the analysis are not required for study entry.)
- Any SAEs directly related to a tumor biopsy procedure should be reported according to Section 9.5

For additional information regarding EGFR T790M testing and biomarker analysis, refer to Section 8.2.2.1 and the Laboratory Manual.

6.1.1.2. Screening (Dose Escalation)

The duration of the Eligibility Screening period is up to 22 days prior to Cycle 0, Day 1 in Dose Escalation.

The following activities and/or assessments should be performed during the screening period:

- Have the subject sign the appropriate ICF before any study-related procedures or assessments are performed. Consent for optional pharmacogenomic (PGx) blood sampling is included in the appropriate ICF.
- Review the subject's demographics, medical and target disease history, and results of tests done as part of routine care and compare against the eligibility criteria (Section 4).
- Perform screening tumor assessments using computed tomography (CT) of the chest, abdomen, and pelvis and other areas of known disease or newly suspected disease. Scans of the abdomen, pelvis, and other areas of the body may be done with magnetic resonance imaging (MRI) (with ≤ 5 mm cuts) instead of CT unless another modality of disease assessment is necessary for the lesion(s), but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. Screening brain scans should be performed by MRI pre- and post- gadolinium or CT with contrast within 22 days prior to C0D-1. A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF) to assess bone metastases should be performed within 6 weeks prior to Cycle0, Day -1 (historical scans within this timeframe are acceptable). Tumor assessments should be performed per RECIST version 1.1 (Section 17.2).
- Assess AEs/SAEs throughout the screening period from the time the subject signed the appropriate ICF (Section 9).
- Ophthalmologic assessments will include visual acuity testing, slit lamp examination, fundoscopy, and tonometry (Section 9.12).
- Perform either ECHO or MUGA. The same test must be used for the subject throughout the study (Section 9.12).
- Perform a complete physical examination including weight and height (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).
- Obtain vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature). SpO_2 (pulse oximetry) should also be obtained. Vital

signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- Obtain triplicate ECGs (approximately 1 minute apart). These ECGs should be reviewed and interpreted on-site by the Investigator for eligibility. Additionally, the ECGs should be submitted to the central laboratory. The mean QTcF of the triplicate set of ECGs will be used to determine eligibility. The ECGs should be measured after the subject has rested supine for at least 10 minutes. (Section 9.10).
- Obtain blood and urine samples for safety analysis (hematology, blood chemistry, coagulation, and urinalysis) (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement.
- Obtain blood for thyroid function tests (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement.
- Perform Hepatitis B (hepatitis B surface antigen [HBsAg], anti-hepatitis B surface antibody [anti-HBs antibody] and anti-hepatitis B core antibody [anti-HBc antibody]), Hepatitis C (hepatitis C virus [HCV] antibody), and HIV antibody tests (HIV antibody test is optional unless required by local regulations or IRB/IECs). As a general rule, blood collection should be conducted after ECG measurement.
- Obtain a serum sample for pregnancy testing in women of child-bearing potential within 7 days before enrollment. For postmenopausal subjects (no child-bearing potential, as indicated by a lapse of at least 12 months since the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc, no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of child-bearing potential and required to undergo pregnancy testing. In case of this procedure and ECG measurement is conducted in the same day, blood collection should be conducted after ECG measurement.
- Record prior medications.
- Subjects should be instructed to take their final dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib 1 day prior to breakfast in clinic on Cycle 0, Day 1, as indicated below:

  2 evenings before breakfast in clinic for Day 1 visit for those subjects who regularly take gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib in the evening

  1 morning before breakfast in clinic for Day 1 visit for those subjects who regularly take gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib in the morning

Refer to Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1) for detailed screening procedures to be conducted.

6.1.2. Cycle 0 (Dose Escalation)

6.1.2.1. Cycle 0, Day 1 (Dose Escalation)

Subjects should report to clinic for collection of baseline ECGs. Refer to Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1) for details of procedures to be performed/obtained.

- Verify that the final dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib was taken 1 day prior to breakfast in clinic on Cycle 0, Day 1.
- Obtain blood for hematology, coagulation, and blood chemistry. As a general rule, this procedure should be conducted after ECG measurement.
- Obtain urine for urinalysis.
- Obtain vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) at specified time points. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- Obtain blood for biomarker analysis (Section 8.2). As a general rule, this procedure should be conducted after ECG measurement.

  Obtain eight 5-mL blood samples for exploratory blood cfDNA biomarker. Refer to the Laboratory Manual for instruction on collection, processing, and shipping of samples.

  Obtain three 3-mL blood samples for exploratory blood biomarkers (osteopontin, IL-8, sAXL) pre-dose as indicated. Refer to the Laboratory Manual for instruction on collection, processing, and shipping of samples.
- Obtain blood sample for pharmacogenomic (PGx) analysis (if subject has consented). As a general rule, this procedure should be conducted after ECG measurement.
- In order to time match with the Cycle 0, Day 1, breakfast should be provided to the subject 30 minutes prior to the planned Day 1 dosing time. Subjects should complete breakfast within approximately 20 minutes although no study drug will be administered on this day (Cycle 0, Day 1). In addition to breakfast time, breakfast content should be the same for Cycle 0, Day 1 and Cycle 0, Day 1.
- Continuous 12-lead Endpoint ECG recording from Holter for the time-matched baseline evaluations:

  ECG extractions will occur as indicated in the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1). 12-lead ECGs will be extracted from a

continuous recording at the nominal time points by the ECG central laboratory.

Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction.

- Lunch should be provided to the subject. Lunch time and content should be the same for Cycle 0, Day 1 and Cycle 0, Day 1.
- Perform a complete physical examination, including weight (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4). Alternatively, this may be performed pre-dose Cycle 0, Day 1.
- Chest radiograph should be performed for safety examination

6.1.2.2. Cycle 0, Day 1 (Dose Escalation)

Day 1 immediately follows Day 1. Subjects should report to the clinic in the morning for pre-dose procedures as indicated in Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1). All procedures should be time matched to procedures obtained/performed on Day 1.

All pre-dose procedures should be completed before breakfast as indicated in Schedule of Events (Table 6.1). The Investigator should review all of the safety laboratories obtained from Cycle 0, Day 1 prior to dosing.

DS-1205c should be administered with 240 mL of water with breakfast. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1):

- Obtain vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) at specified time points. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- Continuous 12-lead ECG recording from Holter for the time-matched endpoint evaluations and safety:

  12-lead Endpoint ECGs will be extracted from a continuous recording at the nominal time points by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Time window for collection time points: -2 hours (for pre-dose) and ±15 minutes (for hours 1 to 8 post-dose).

Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.

- Obtain blood sample for PK analysis of DS-1205a at all specified time points. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: ±15 minutes of nominal times.
- If not completed on Cycle 0, Day 1, perform a complete physical examination, including weight (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).
- Lunch should be provided to the subject approximately 4 hours after dosing. Lunch time and content should be the same for Cycle 0, Day 1 and Cycle 0, Day 1.
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

After completion of 10-hour post-dose PK blood sample collections, subjects should be given dinner in the clinic. Dinner should be started approximately 30 minutes prior to dosing and should be completed before dosing. Subjects should receive the evening dose of DS-1205c in the clinic with 240 mL of water.

6.1.2.3. Cycle 0, Day 2 (Dose Escalation)

All pre-dose procedures should be completed before breakfast as indicated in Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1). The Investigator should review all of the pre-dose results prior to dosing, including safety laboratories results (eg, blood chemistry, hematology, and urinalysis).

DS-1205c should be administered with 240 mL of water following breakfast. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1):

- Obtain vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) pre-dose. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- 12-lead Endpoint ECGs will be extracted from a continuous recording pre-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Time window for collection time points: -2 hours of nominal times (for pre dose).
- Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood sample for PK analysis of DS-1205a pre-dose. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours of nominal times (for pre dose).
- Obtain blood for hematology, coagulation, and blood chemistry pre-dose. As a general rule, this procedure should be conducted after ECG measurement. If this procedure need to be done before ECG measurement, investigators should contact Sponsor for guidance scheduling of these procedures.
- Obtain urine for urinalysis pre-dose.
- Perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

6.1.2.4. Cycle 0, Day 4 (Dose Escalation)

All pre-dose procedures should be completed before breakfast on Day 4 (±1 day) as indicated in Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1).

DS-1205c should be administered with 240 mL of water following breakfast. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1):

- Obtain vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) pre-dose. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- 12-lead Endpoint ECGs will be extracted from a continuous recording pre-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Time window for collection time points: -2 hours of nominal times (for pre-dose).
- Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood sample for PK analysis of DS-1205a pre-dose. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours of nominal times (for pre-dose).
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

6.1.2.5. Cycle 0, Day 6 (Dose Escalation)

All pre-dose procedures should be completed before breakfast as indicated in Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1). The Investigator should review all of the safety laboratories obtained from Cycle 0, Day 6 (eg, blood chemistry, hematology, and urinalysis) prior to dosing.

DS-1205c should be administered with 240 mL of water following breakfast. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1):

- Obtain vital signs (systolic and diastolic blood pressure, and HR) pre-dose. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- Obtain blood for hematology, coagulation, and blood chemistry pre-dose. As a general rule, this procedure should be conducted after ECG measurement. If this procedure need to be done before ECG measurement, investigators should contact Sponsor for guidance scheduling of these procedures.
- Obtain urine for urinalysis pre-dose.

- 12-lead Endpoint ECGs will be extracted from a continuous recording pre-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Time window for collection time points: 2 hours of nominal times (for pre-dose).
- Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood sample for PK analysis of DS-1205a pre-dose. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours of nominal times (for pre dose).
- Perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

6.1.2.6. Cycle 0, Day 7 (Dose Escalation)

All pre-dose procedures should be completed before breakfast as indicated in Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1). The Investigator should review all of the safety laboratories obtained from Cycle 0, Day 7 prior to dosing.

DS-1205c should be administered with 240 mL of water following breakfast. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 0) (Table 6.1):

- Obtain vital signs (systolic and diastolic blood pressure, and HR) pre-dose. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- 12-lead Endpoint ECGs will be extracted from a continuous recording at the nominal time points by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Time window for collection time points: 2 hours (for pre dose) and ±15 minutes (for hours 1 to 8 post-dose) of nominal times.

- Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood sample for PK analysis of DS-1205a. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours (for pre-dose) and ±15 minutes (for hours 1 to 10 post-dose) of nominal times.
- Obtain blood for hematology, coagulation, and blood chemistry pre-dose (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures. Alternatively, blood for hematology, coagulation, and blood chemistry may be obtained Cycle 1, Day 1.
- Obtain blood for thyroid function tests (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures. Alternatively, blood for thyroid function tests may be obtained Cycle 1, Day 1.
- Obtain urine for urinalysis before breakfast. Alternatively, urine for urinalysis may be obtained Cycle 1, Day 1.
- Perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4). Alternatively, a complete physical examination and functional status may be performed/recorded Cycle 1, Day 1.
- Lunch should be provided to the subject approximately 4 hours after dosing. Lunch time and content should be the same as on Cycle 0, Day -1.
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Determine whether AEs/SAEs require delay of Cycle 1 dosing (Section 5.4.1).
- Record concomitant medications.

After completion of 10-hour post-dose PK blood sample collections, subjects should be given dinner in the clinic. Dinner should be started approximately 30 minutes prior to dosing and should be completed before dosing. Subjects should receive the evening dose of DS-1205c in the clinic with 240 mL of water.

6.1.3. Cycle 1 and Beyond (Dose Escalation)

Subjects should continue to take DS-1205c orally BID (approximately 12 hours apart). Beginning in Cycle 1, gefitinib 250 mg should be co-administered orally QD with the morning DS-1205c dose. Cycle 1 and subsequent cycles are 21-day cycles (see Section 3.2.1.2 for dose selection).

Procedures to be conducted on each visit day for Dose Escalation are outlined in the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2).

6.1.3.1. Cycle 1, Day 1 (Dose Escalation)

Cycle 1, Day 1 immediately follows Cycle 0, Day 7. Subjects should report to the clinic in the morning.

Subjects should be given breakfast in the clinic. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1. Subjects should receive the morning dose of DS-1205c and 250 mg of gefitinib with 240 mL of water.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2):

- Vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) and SpO_2 (pulse oximetry), at pre-dose and at 2, 4, 6, and 8 hours post-dose. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- If not obtained on Cycle 0, Day 7, obtain blood for hematology, coagulation, and blood chemistry before breakfast (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- If not obtained on Cycle 0, Day 7, obtain blood for thyroid function tests (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- If not obtained on Cycle 0, Day 7, obtain urine for urinalysis before breakfast .
- Endpoint ECGs: 12-lead ECGs will be extracted from a continuous recording at pre-dose and at 2, 4, 6, and 8 hours post-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after ECG extraction.
- Safety ECGs: 12-lead ECG recordings should be printed at pre-dose and at 2, 4, 6, and 8 hours post-dose for on-site safety assessment by the Investigator

and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.

- Obtain blood samples for PK analysis, pre-dose, for both DS-1205a and gefitinib. All PK blood draws should be performed as close as possible to scheduled time. The PK specimen should be taken immediately after completion of the Endpoint ECG. Time window for collection time points: 2 hours (for pre-dose), ±15 minutes (for hours 2 to 8 post-dose), and ±2 hours (for 24 hours post-dose) of nominal times.
- Obtain blood sample for Exploratory Blood cfDNA pre-dose. As a general rule, this procedure should be conducted after ECG measurement.
- Obtain blood sample for Exploratory Blood Biomarker pre-dose. As a general rule, this procedure should be conducted after ECG measurement.
- If not performed/recorded on Cycle 0, Day 7, perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Appendix 17.4).
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

6.1.3.2. Cycle 1, Day 4, Day 8, and Day 15 (Dose Escalation)

Subjects should report back to the clinic in the morning to receive breakfast and doses of DS-1205c and gefitinib, and procedures should be obtained/performed on Day 4, Day 8, and Day 15 (±1 day) as indicated per the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2):

Subjects should be given breakfast in the clinic. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1. Subjects should receive the morning dose of DS-1205c and 250 mg of gefitinib with 240 mL of water.

- Obtain blood for hematology, coagulation, and blood chemistry. As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain urine for urinalysis.
- Vital signs (systolic and diastolic blood pressure, HR) and SpO_2 (pulse oximetry) pre-dose. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- Endpoint ECGs: 12-lead ECGs will be extracted from a continuous recording pre-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after ECG extraction. Time window for collection time points: 2 hours of nominal times.
- Safety ECGs: 12-lead ECG recordings should be printed pre-dose for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood samples for PK analysis, pre-dose, for both DS-1205a and gefitinib. All PK blood draws should be performed as close as possible to scheduled time. The PK specimen should be taken immediately after completion of the Endpoint ECG. Time window for collection time points: 2 hours of nominal times.
- Obtain blood sample for Exploratory Blood Biomarker pre-dose. As a general rule, this procedure should be conducted after ECG measurement.
- Perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Appendix 17.4).
- Assess AEs/SAEs (Section 9).
- During the DLT-evaluation period (from Cycle 0, Day 1 to Cycle 1, Day 21 of Dose Escalation), determine whether AEs/SAEs represent DLT (Section 3.2.1.3).
- Record concomitant medications.

Day 15 only:

- An optional On-Study tumor biopsy may also be performed on Cycle 1, Day 15(+7 days). Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy may be obtained from primary tumor or metastatic site.

6.1.3.3. Cycle 2, Day 1 (Dose Escalation)

Subjects should report to the clinic in the morning.

Subjects should be given breakfast in the clinic. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1. Subjects should receive the morning dose of DS-1205c and 250 mg of gefitinib with 240 mL of water.

The following procedures should be obtained/performed on Day 1 (±1 day) per the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2):

- Obtain blood for hematology, coagulation, and blood chemistry. As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.

- Obtain blood for thyroid function tests (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain urine for urinalysis.
- Vital signs (systolic and diastolic blood pressure, HR, respiratory rate, and body temperature) and SpO_2 (pulse oximetry), pre-dose. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- Endpoint ECGs: 12-lead ECGs will be extracted from a continuous recording at pre-dose and at 2, 4, 6 and 8 hours post-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction.
- Safety ECGs: 12-lead ECG recordings should be printed at pre-dose and at 2, 4, 6 and 8 hours post-dose for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point. Time window for collection time points: 2 hours (for pre-dose), ±15 minutes (for hours 1 to 10 post-dose), and ±2 hours (for 24 hours post-dose) of nominal times.
- Lunch should be provided to the subject approximately 4 hours after dosing. Lunch time and content should be the same for Cycle 2, Day 1 as Cycle 0, Day 1.
- Obtain blood samples for PK analysis for both DS-1205a and gefitinib at all specified time points within Table 6.2. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours (for pre-dose), ±15 minutes (for hours 1 to 10 post-dose), and ±2 hours (for 24 hours post-dose) of nominal times.
- Obtain blood sample for Exploratory Blood cfDNA pre-dose. As a general rule, this procedure should be conducted after ECG measurement.
- Obtain blood sample for Exploratory Blood Biomarker pre-dose. As a general rule, this procedure should be conducted after ECG measurement.
- Perform a complete physical examination, including weight (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).
- Ophthalmologic evaluation should be performed within 7 days of the scheduled visit. Assessments should include visual acuity testing, slit lamp examination, fundoscopy, and tonometry (Section 9.12).

- Perform either ECHO or MUGA within 7 days of the scheduled visit. The same test must be used for the subject throughout the study (Section 9.12).
- Assess AEs/SAEs (Section 9).
- Record concomitant medications.

After completion of 10-hour post-dose PK blood sample collections, subjects should be given dinner in the clinic. Dinner should be started approximately 30 minutes prior to dosing and should be completed before dosing. Subjects should receive the evening dose of DS-1205c in the clinic with 240 mL of water.

6.1.3.4. Cycle 2, Day 2 and Day 8 (Dose Escalation)

Subjects should report back to the clinic in the morning to receive breakfast and doses of DS-1205c and gefitinib, and procedures should be obtained/performed on Day 2, and Day 8 (± 1 day) as indicated per the Schedule of Events, Dose Escalation (Cycle 1 and beyond) (Table 6.2):

Subjects should be given breakfast in the clinic. Breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes on Day 2. In addition to breakfast time, breakfast content should be the same as on Cycle 0, Day -1. On Day 8, it is recommended to finish breakfast within approximately 30 minutes, and DS-1205c should be taken right after meal completion. Subjects should receive the morning dose of DS-1205c and 250 mg of gefitinib with 240 mL of water.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 1 and beyond) (Table 6.2):

- Obtain vital signs (systolic and diastolic blood pressure, and HR) pre-dose. SpO_2 (pulse oximetry) should also be obtained. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.
- Safety ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Assess AEs/SAEs (Section 9).
- Record concomitant medications.

Day 2 only:

- 12-lead Endpoint ECGs will be extracted from a continuous recording pre-dose by the ECG central laboratory. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point for ECG extraction.
- Obtain blood samples for PK analysis of DS-1205a and gefitinib pre-dose. All PK blood draws should be performed as close as possible to scheduled time. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG.

Day 8 only:

- Obtain blood for hematology, and blood chemistry pre-dose. As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Perform a complete physical examination (Section 9.11), and assess and record the functional status using the ECOG PS scale (Section 17.4).

After completion of in-clinic procedures of Cycle 2, Day 2, subjects should be discharged from the clinic with study medications for at-home dosing and the Study Medication Diary. Subjects should be reminded to bring all study medications and Study Medication Diary the following day.

- Instructions for at-home dosing of DS-1205c and gefitinib (including this evening's dose of DS-1205c) and timing of doses relative to meals. Refer to the Pharmacy Instructions for detailed instructions.
- Instructions for completion of the Study Medication Diary.
- Reminder to bring all study medications and Study Medication Diary to every subsequent visit.

Subjects should be instructed to not take morning doses at home on study visit days; they will take these doses in clinic instead, coordinated with appropriate pre-dose and post-dose procedures.

6.1.3.5. Tumor Assessments (Dose Escalation)

- Investigator determined tumor assessments of the chest, abdomen, and pelvis and other areas where scans were performed at screening or newly suspected disease should be performed every 6 weeks (±7 days) from Cycle 1, Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments should be used throughout the study for all assessments for each subject unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 Tumor assessments should be performed per RECIST version 1.1 (Section 17.2). SpO_2 should also be measured at the time of tumor assessment per Investigator discretion.
- Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Perform CT or MRI of the brain in subjects with baseline brain metastases or if clinically indicated, and within a target of 1 week after a subject achieves a CR. A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF) to assess bone metastases should be performed every 24 weeks (within that 24th week)

from C1D1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan will be required at confirmation of CR to exclude new bone metastases. Lesions detected on bone scans must be followed with cross-sectional imaging.

6.1.3.6. Chest Radiograph for Safety Evaluation (Dose Escalation)

- Investigator should perform chest radiograph in Cycle 0 Day -1, Cycle 2, Day 1 and Cycle 4, Day 1 (±2days) for safety evaluation.

6.1.3.7. Cycle 3 and Subsequent Cycles, Day 1 (Dose Escalation)

Subjects should report to the clinic in the morning.

Subjects should be given breakfast in the clinic. It is recommended that breakfast be completed approximately 30 minutes; DS-1205c should be taken immediately after meal completion. Subjects should receive the morning dose of DS-1205c and 250 mg of gefitinib with 240 mL of water.

The following procedures should be obtained/performed on Day 1 (±2 day) per the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2):

- Ophthalmologic evaluation should be performed. Assessments should include visual acuity testing, slit lamp examination, fundoscopy, and tonometry (Section 9.12). Assessments should be conducted on Day 1 of Cycle 4 and every 4 cycles (–7 days) thereafter (Cycles 8, 12, 16…).
- Perform either ECHO or MUGA. The same test must be used for the subject throughout the study (Section 9.12). Assessments should be conducted on Day 1 of Cycle 4 and every 4 cycles (7 days) thereafter (Cycles 8, 12, 16…).
- Obtain blood for hematology and blood chemistry (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain blood for coagulation (Day 1 of Cycle 3 and every 2 cycles thereafter: Cycles 5, 7, 9…) (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain blood for thyroid function tests (Day 1 of Cycle 3 and every 2 cycles thereafter: Cycles 5, 7, 9…) (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Vital signs (systolic and diastolic blood pressure, HR) and SpO_2 (pulse oximetry), pre-dose. Vital signs should be measured in the resting state

(Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- Safety ECGs: 12-lead ECG recordings should be printed for on-site safety assessment by the Investigator and for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
- Obtain blood sample pre-dose for PK analysis for DS-1205a. When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Time window for collection time points: 2 hours of nominal times.
- Obtain blood sample for Exploratory Blood cfDNA pre-dose (Day 1 of Cycle 3 and every two cycles thereafter: Cycles 5, 7, 9…). As a general rule, this procedure should be conducted after ECG measurement.
- Obtain blood sample for Exploratory Blood Biomarker pre-dose (Day 1 of Cycle 3 and every two cycles thereafter: Cycles 5, 7, 9…). As a general rule, this procedure should be conducted after ECG measurement.
- Perform a complete physical examination, including weight (Section 9.11), and assess and record the functional status using the ECOG PS scale (Appendix 17.4).
- Assess AEs/SAEs (Section 9).
- Record concomitant medications.
- Instructions for at-home dosing of DS-1205c and gefitinib (including this evening's dose of DS-1205c) and timing of doses relative to meals. Refer to the Pharmacy Instructions for detailed instructions.
- Instructions for completion of the Study Medication Diary.
- Reminder to bring all study medications and Study Medication Diary to every subsequent visit.

Subjects should be instructed to not take morning doses at home on study visit days; they will take these doses in clinic instead, coordinated with appropriate pre-dose and post-dose procedures.

6.1.3.8. End-of-Treatment (EOT) Visit (Dose Escalation)

This visit occurs within 7 days after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first.

The following procedures should be obtained/performed per the Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Table 6.2):

- Vital signs (systolic and diastolic blood pressure, HR) and SpO_2 (pulse oximetry), pre-dose. Vital signs should be measured in the resting state (Section 9.9). This procedure should not be conducted during the supine position for ECG measurement.

- Safety ECGs: 12-lead ECG recordings should be printed for on-site safety assessment by the Investigator. Subjects should be resting supine for at least 10 minutes prior to and 5 minutes after ECG extraction.
- Obtain blood for hematology and blood chemistry. As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain blood for coagulation (Section 9.8). As a general rule, this procedure should be conducted after ECG measurement. If this procedure needs to be done before ECG measurement, investigators should contact Sponsor for guidance in scheduling of these procedures.
- Obtain urine for urinalysis.
- Obtain a urine sample for pregnancy testing in women of child-bearing potential.
- Obtain blood sample for Exploratory Blood cfDNA. As a general rule, this procedure should be conducted after ECG measurement.
- Obtain blood sample for Exploratory Blood Biomarker. As a general rule, this procedure should be conducted after ECG measurement.
- Perform a complete physical examination, including weight (Section 9.11), and assess and record the functional status using the ECOG PS scale (Appendix 17.4).
- Perform radiographic tumor assessments (CT/MRI) of the chest, abdomen and pelvis and all sites of disease, as per RECIST version 1.1 (Section 17.2). If the previous scan was obtained within the last 6 weeks, this assessment does not need to be performed at the EOT visit.
- Ophthalmologic evaluation should be performed. Assessments should include visual acuity testing, slit lamp examination, fundoscopy, and tonometry (Section 9.12). Assessments may be performed with a window of up to 7 days prior.
- Perform either ECHO or MUGA. The same test must be used for the subject throughout the study (Section 9.12). Assessments may be performed with a window of up to 7 days prior.
- Assess AEs/SAEs (Section 9).
- Record concomitant medications.
- Optional EOT tumor biopsy. Tumor biopsy should be obtained from primary tumor or metastatic site, preferably from a site of recent radiographic progression, within 30 days of the last dose of study drug, and prior to starting any new anticancer treatment.

6.1.3.9. Follow-Up Call (Dose Escalation)

A follow-up telephone call to the subject to review AEs/SAEs (Section 9) should occur 30 days (+7 days) after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first.

6.1.3.10. New Cancer Treatment and Survival Follow-up (Dose Escalation)

After discontinuation from study treatment, follow-up information for survival and subsequent anticancer therapy, if available, should be obtained every 3 months (±30 days) from the date of the follow-up visit or Safety Follow-up, whichever is later, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first. If direct contacts are not possible due to withdrawal of consent or loss to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws.

6.2. CCI

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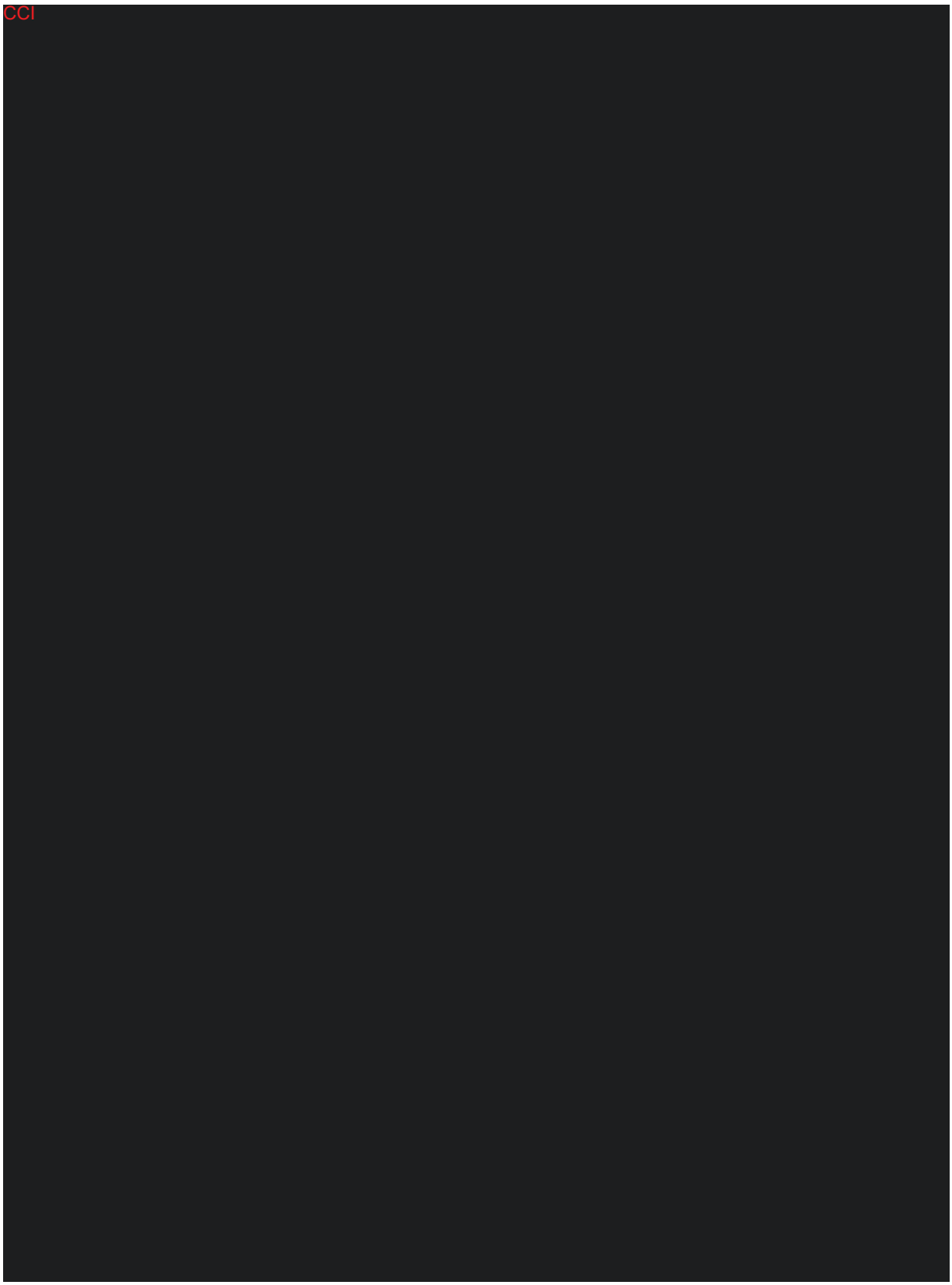

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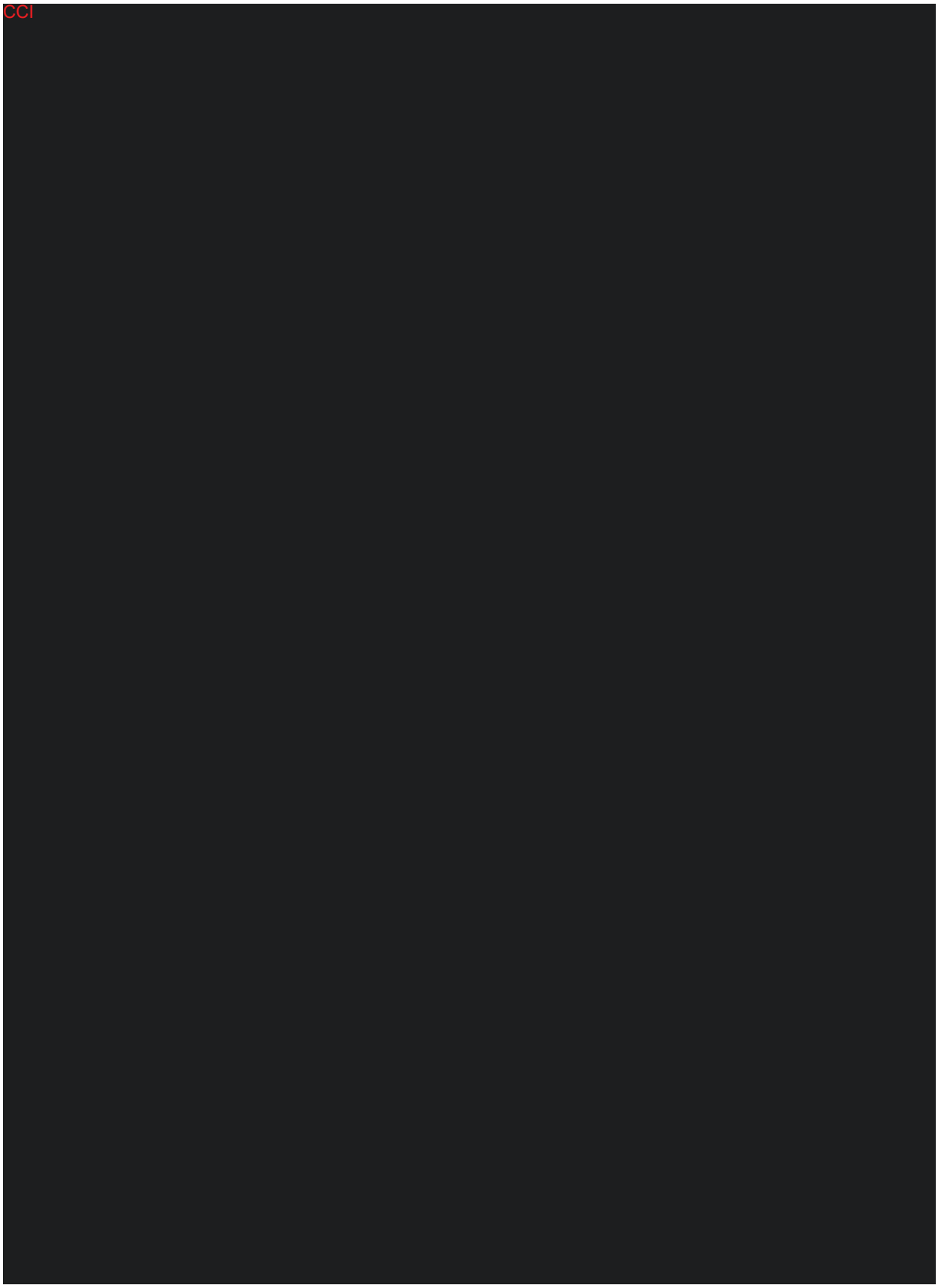

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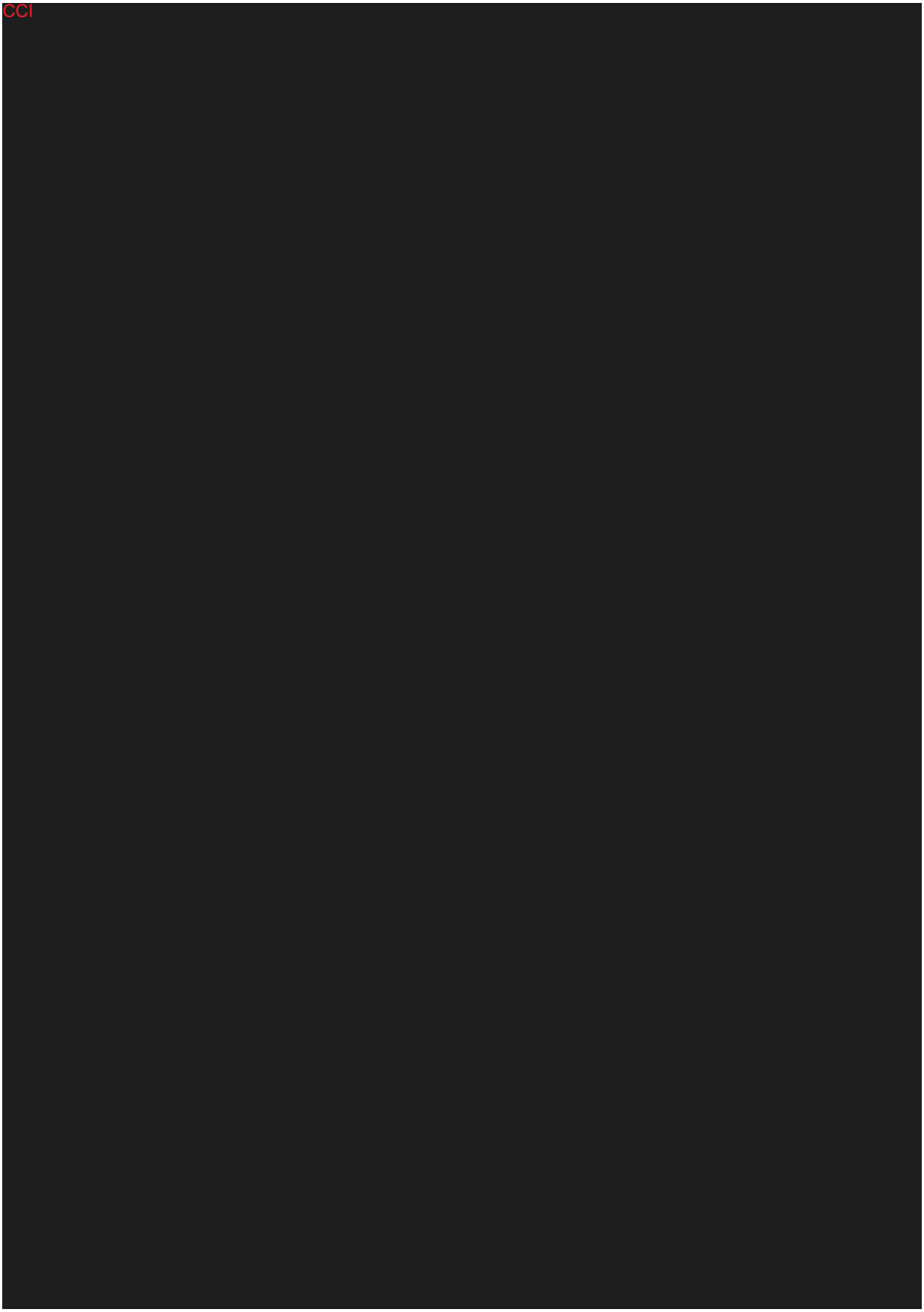

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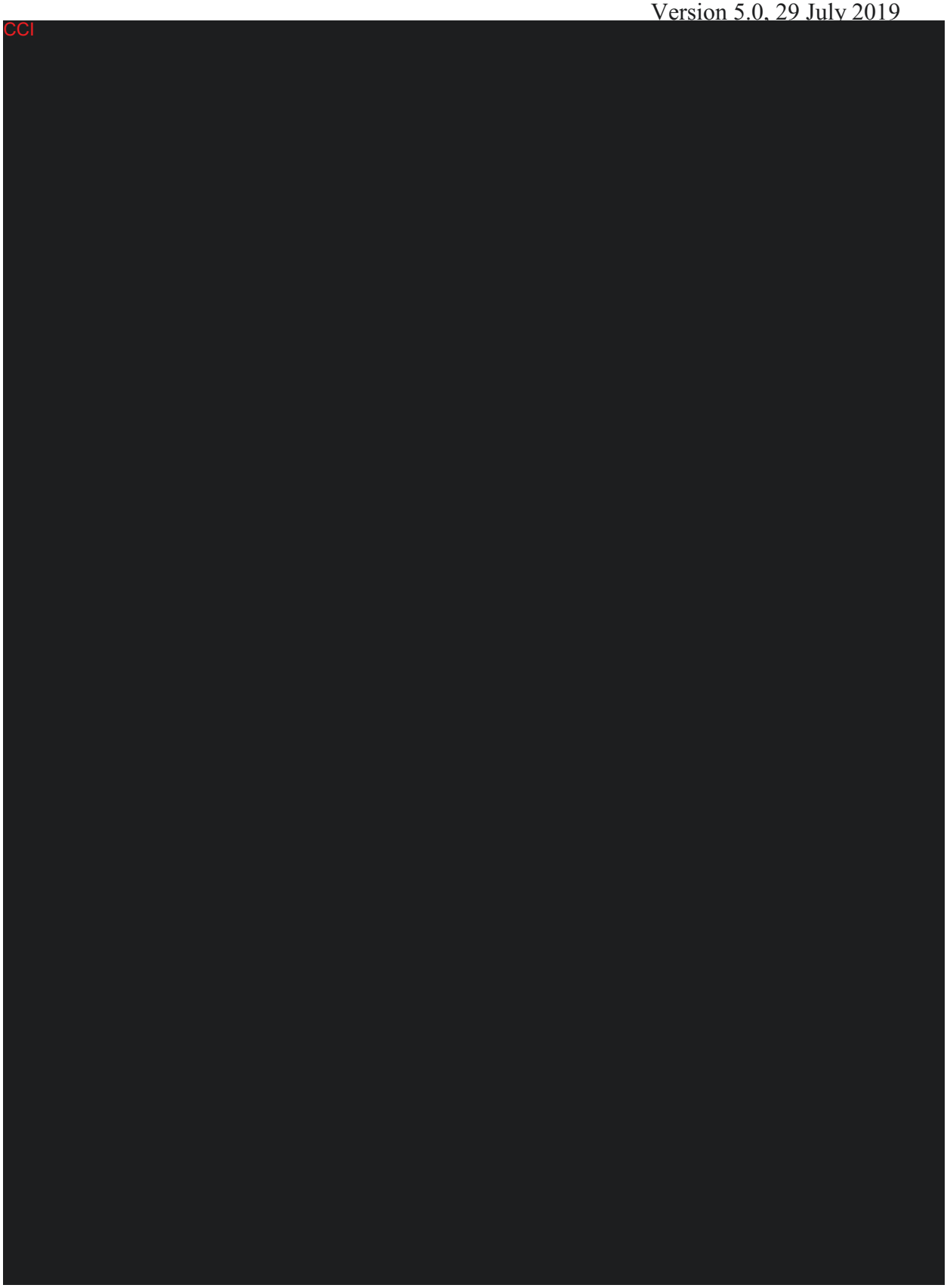

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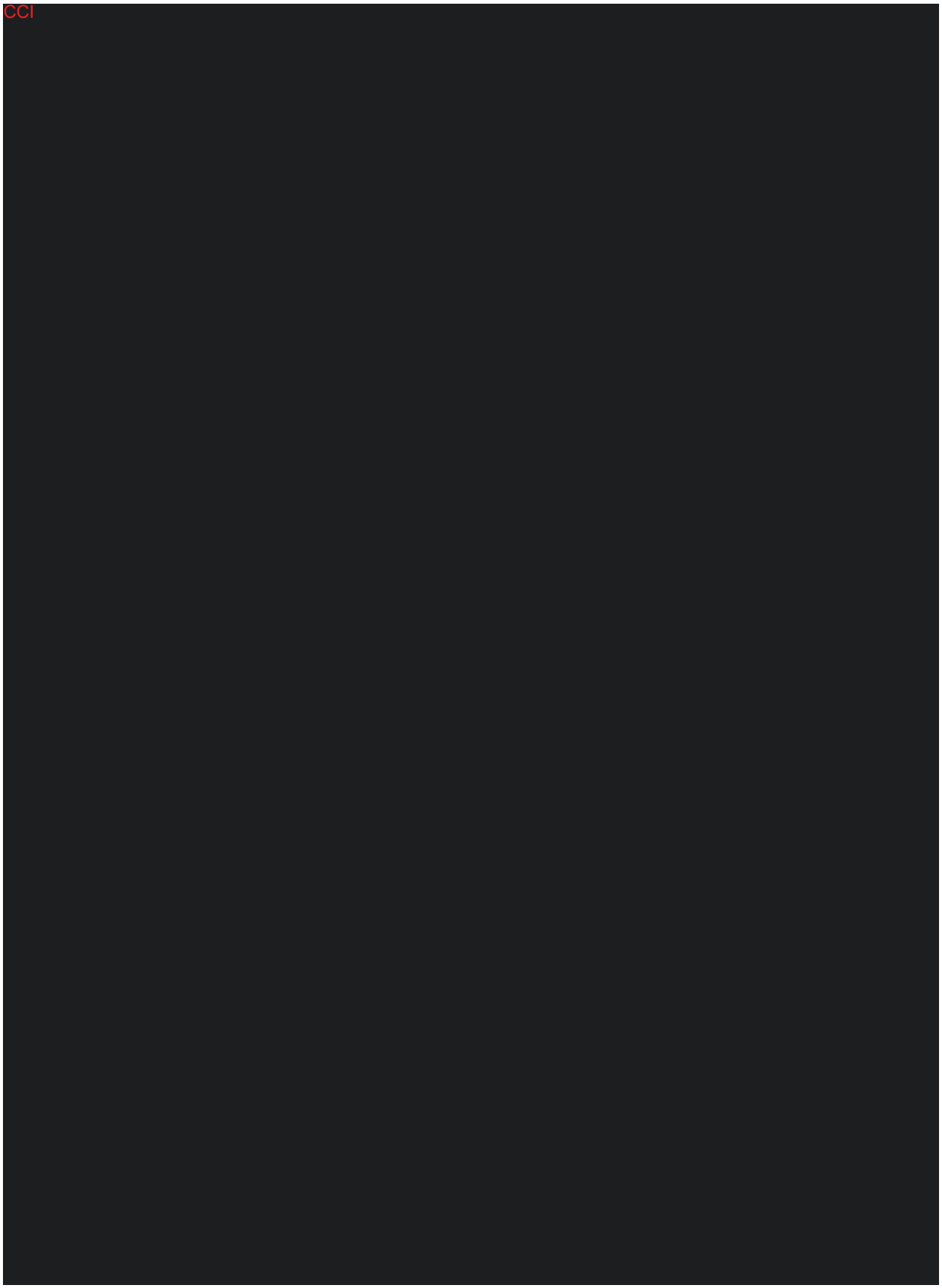

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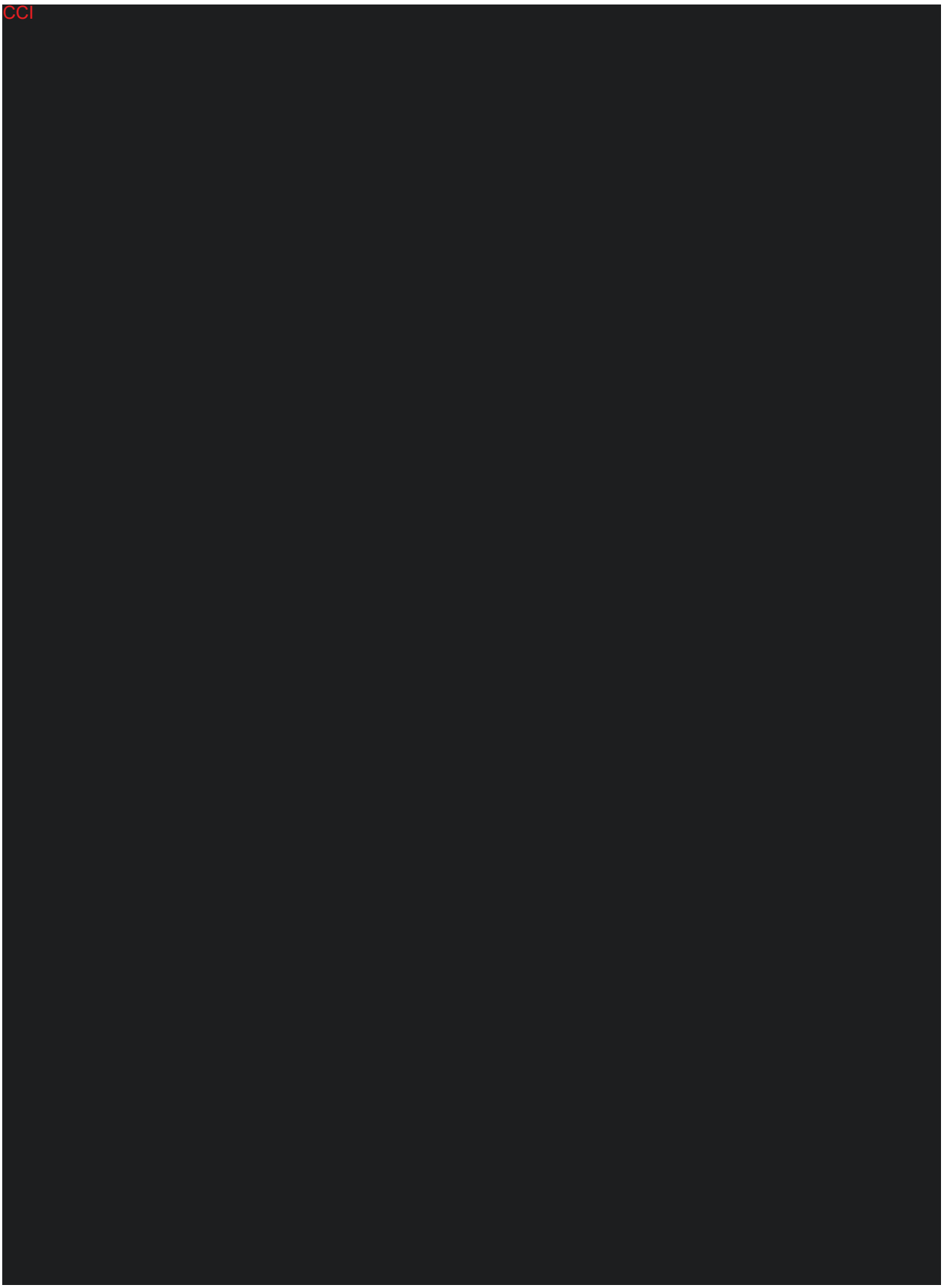

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6.3. Schedule of Events

The schedule of study events is provided for Dose Escalation in Table 6.1 andTable 6.2 and for Dose Expansion in Table 6.3.

Table 6.1: Schedule of Events, Dose Escalation (Cycle 0)

Visit Description	Screening		Treatment and Evaluations[a]																								
	Tissue	Eligibility																									
CYCLE			Cycle 0																								
DAY			1[a]						1[a]								2	4	6	7							
HOUR			Pre[b]	0	2	4	6	8	Pre[c]	0	1	2	4	6	8	10		(±1D)		Pre[c]	0	1	2	4	6	8	10
Informed Consent[d]	X	X																									
Archived Tumor Tissue	X																										
Fresh Tumor Biopsy[e]	X																										
Demographics		X																									
Medical History		X																									
Final Dose of Gefitinib, Erlotinib, Afatinib, Dacomitinib, or Osimertinib		X[f]																									
Inclusion/ Exclusion Criteria		X																									
ECHO/ MUGA		X																									
Hematology and Blood Chemistry Tests[g]		X	X[h]														X[c]		X[c]	X[i]							
Coagulation		X	X[h]														X[c]		X[c]	X[i]							
Thyroid Function Tests (T3[FT3], T4[FT4], and TSH)		X																		X[i]							
Pregnancy Test		X[j]																									
Urinalysis		X	X[h]														X[c]		X[c]	X[i]							

Table 6.1: Schedule of Events, Dose Escalation (Cycle 0) (Continued)

Visit Description	Screening		Treatment and Evaluations[a]																							
	Tissue	Eligibility																								
CYCLE			Cycle 0																							
DAY			1[a]						1[a]								2	4	6	7						
HOUR			Pre[b]	0	2	4	6	8	Pre[c]	0	1	2	4	6	8	10		(±1D)		Pre[c]	0	1	2	4	6	8	10
Hepatitis B, Hepatitis C, and HIV Antibody Tests[k]		X																								
12 Lead Safety ECG[l]		X[m]							X		X	X	X	X	X		X[c]	X[c]	X[c]	X		X	X	X		X	
12 Lead Endpoint ECG[n]			X		X	X	X	X	X			X	X	X	X		X[c]	X[c]	X[c]	X			X	X	X	X	
Vital Signs/Pulse Oximetry[o]		X	X						X		X		X	X	X		X[c]	X[c]	X[c]	X							
Height		X																									
Weight		X	X[p]						X[p]																		
Physical Examination/ ECOG PS		X	X[p]						X[p]								X[c]		X	X[i]							
Ophthalmologic Assessments[q]		X																								
Breakfast In Clinic[r s]			X						X								X	X	X	X							
DS 1205c Administration In Clinic (morning dose)[t]										X							X	X	X		X						
Lunch In Clinic[s]						X							X											X			
Dinner In Clinic[r s]																X											X
DS 1205c Administration In Clinic (evening dose)[t]																X											X

Table 6.1: Schedule of Events, Dose Escalation (Cycle 0) (Continued)

Visit Description	Screening		Treatment and Evaluations[a]																									
	Tissue	Eligibility																										
CYCLE			Cycle 0																									
DAY			D 1[a]						D1[a]								D 2	D 4	D 6	D7								
HOUR			Pre[b]	0	2	4	6	8	Pre[c]	0	1	2	4	6	8	10		(±1D)		Pre[c]	0	1	2	4	6	8	10	
Tumor Assessment (CT/MRI)[u]		X[v]																										
Chest Radiograph for Safety Examination			X																									
Bone Scan		X[w]																										
PGx Blood Sample (optional)[x]			X																									
Exploratory Blood cfDNA Sample[y]			X																									
Exploratory Blood Biomarker Sample[z]			X																									
DS 1205a PK Blood Sample[aa]									X		X	X	X	X	X	X	X[c]	X[c]	X[c]	X		X	X	X	X	X	X	
Adverse Events	X[bb]																											
Prior/ Concomitant Medications		X																										

cfDNA cell free DNA; CT computed tomography; D Day; ECG electrocardiogram; ECHO echocardiography; ECOG Eastern Cooperative Oncology Group; EGFR epidermal growth factor receptor; HIV human immunodeficiency virus; LVEF left ventricular ejection fraction; MRI magnetic resonance imaging; MUGA multigated acquisition scan; PGx pharmacogenomics; PK pharmacokinetic(s); Pre pre dose; PS performance status; SpO_2 peripheral capillary oxygen saturation; T3 triiodothyronine; T4 thyroxine; TKI tyrosine kinase inhibitor; TSH thyroid stimulating hormone

Table 6.1: Schedule of Events, Dose Escalation (Cycle 0) (Continued)

a. Time points on Day 1 should be time matched to Day 1 (eg, Hour 0 on Day 1 should occur at the same clock time as Hour 0 on Day 1, when study drug is scheduled to be administered). Time matched endpoints: pre dose procedures, Endpoint ECGs, and meals. Exception: the Cycle 0, Day 1 10h time point has no match on Cycle 0, Day 1.A second subject in each dosing level should start dosing at least 24 hours after the initial dosing of the first subject.
aa. All PK blood draws should be performed as close as possible to the scheduled time, with windows of 2 hours (for pre dose),and ±15 minutes (for hours 1 to 10 post dose). When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. Refer to the Laboratory Manual for instructions about collection, processing, and shipping of samples.
b. Pre dose on Cycle 0, Day 1 is a time point matched to Cycle 0, Day 1. No study drug is to be administered on Cycle 0, Day 1. The meal time for Day 1 and Day 1 should be the same in order to obtain matched time points. Pre dose procedures are to be obtained prior to starting breakfast. Exception: the Cycle 0, Day 1 10h time point has no match on Cycle 0, Day 1.
bb. Any SAEs directly related to a tumor biopsy procedure performed after signing the appropriate ICF should be reported.
c. Pre dose procedures are to be obtained/performed prior to starting in clinic meal (breakfast).
d. Informed consent should be obtained at screening prior to performing any study related procedures. Subjects need to sign a separate ICF for tissue screening.
e. Fresh tumor biopsy is required for subjects who have not had a tumor biopsy since progression while on gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib; and for subjects who lack sufficient archival tumor tissue from a tumor biopsy since progression while on gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.
f. Subjects must take their final dose of gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib between 20 to 36 hours prior to breakfast in clinic on Cycle 0, Day 1.
g. Blood samples for safety laboratories should be collected and creatinine clearance will be estimated at the Screening Visit. As a general rule, blood collection should be conducted after ECG measurement.
h. Results are required prior to dosing on Cycle 0, Day 1.
i May be obtained/performed pre dose on Cycle 1, Day 1.
j. Within 7 days before enrollment. In case of this procedure and ECG measurement is conducted in the same day, blood collection should be conducted after ECG measurement.
k. Perform Hepatitis B (HBsAg, anti HBs antibody and anti HBc antibody), Hepatitis C (HCV antibody), and HIV antibody tests (HIV antibody test is optional unless required by local regulations or IRB/IECs). As a general rule, blood collection should be conducted after ECG measurement.
l. Safety ECG recordings should be printed for on site safety assessment by the Investigator and submitted for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point. Refer to ECG Manual for additional information.
m. Obtain triplicate ECGs (approximately 1 minute apart). These ECGs should be reviewed and interpreted on site by the Investigator for eligibility. The mean QTc of the triplicate set of ECGs will be used to determine eligibility. Additionally, the ECGs should be submitted to the central laboratory.
n. At every time point specified for 12 Lead Endpoint ECGs, 3 Holter derived ECGs will be extracted by the central ECG laboratory. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point. When an ECG is performed at the same study time point as a PK sample, the PK sample should be taken immediately afterward. Refer to Investigator Site Manual for additional information.
o. Vital sign measurements include systolic/diastolic blood pressure and HR. Pulse oximetry should be performed with vital signs. Respiratory rate and body temperature should also be measured at Screening and pre dose Day 1 and Day 1; then at 24h post dose (Day 2) and 72h post dose (Day 4). Vital signs should be measured in the resting state. This procedure should not be conducted during the supine position for ECG measurement.
p. Physical examination/ECOG PS and weight need to be obtained/performed on EITHER Cycle 0, Day 1 or Cycle 0, Day 1.
q. Ophthalmologic assessments: visual acuity, slit lamp examination, fundoscopy, and tonometry. More frequent examinations may be performed at the discretion of the Investigator.
r. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS 1205c should be taken immediately after meal completion. Doses of DS 1205c should be taken approximately 12 hours apart.
s. Meals administered in the clinic on Days 1, 2, 4, 6, and 7 should be time matched to, and contain similar contents as meals administered on Day 1. Lunch can be given approximately 4 hours after dosing.
t. DS 1205c should be administered BID, with 240 mL of water. DS 1205c should be administered 30 minutes following the start of the meal (breakfast or dinner) and after all other pre dose procedures have been performed.

Table 6.1: Schedule of Events, Dose Escalation (Cycle 0) (Continued)

u. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments should be used throughout the study for all assessments for each subject unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1. Tumor assessments should be performed per RECIST version 1.1.
v. CT or MRI of the brain should be performed for all subjects.
w. A bone scan (99m technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F NaF) to assess bone metastases should be performed within 6 weeks prior to Cycle 0, Day 1 (historical scans are acceptable).
x. Consent for pharmacogenomic (PGx) blood sampling is included in the main study ICF. As a general rule, blood collection should be conducted after ECG measurement.
y. Obtain eight 5 mL samples for exploratory pharmacodynamic biomarkers (cfDNA and exosomes). As a general rule, blood collection should be conducted after ECG measurement. Refer to the Laboratory Manual for instructions for collection, processing, and shipping of samples.
z. Obtain three 3 mL samples for pharmacodynamic biomarkers (osteopontin, IL 8, sAXL) pre dose as indicated. As a general rule, blood collection should be conducted after ECG measurement. Refer to the Laboratory Manual for instructions for collection, processing, and shipping of samples.

Table 6.2: Schedule of Events, Dose Escalation (Cycle 1 and Beyond)

Visit Description	Treatment and Evaluation																
CYCLE	**Cycle 1**				**Cycle 2**										**Cycle 3 & Subsequent Cycles**	**EOT[a]**	**q3 mo F/U**
Cycle Length (days)	**21**				**21**										**21**		
DAY	**C1 D1**	**C1 D4**	**C1 D8**	**C1 D15**	**C2 D1**								**C2 D2**	**C2 D8**	**Cn D1**		
Visit Window (days)		**±1**	**±1**	**±1**	**±1**									**± 1**	**±2**	**+7**	**±30**
HOUR					**Pre-dose**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**24**				
Hematology and Blood Chemistry Tests[b]	X[c]	X	X	X	X									X	X	X	
Coagulation Tests[b]	X[c]	X	X	X	X										X Day 1 of Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9...)	X	
Thyroid Function Tests (T3[FT3], T4[FT4], and TSH)	X[c]				X[b]										X[b] Day 1 of Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9...)		
Pregnancy Test																X	
Urinalysis[b]	X[c]	X	X	X	X											X	
12 Lead Safety ECGs[d]	X[e]	X[b]	X[b]	X[b]	X			X	X	X	X		X[b]	X[b]	X[b]	X	
12 Lead Endpoint ECGs[f]	X[e]	X[b]	X[b]	X[b]	X			X	X	X	X		X[b]				
Weight					X										X[b]	X	
Vital Signs/Pulse Oximetry[g]	X[e]	X[b]	X[b]	X[b]	X								X[b]	X[b]	X[b]	X	
Physical Examination/ECOG PS[b]	X[c]	X	X	X	X									X	X	X	
Breakfast In Clinic[h,i]	X	X	X	X	X								X	X	X		
DS 1205c Administration In Clinic (morning dose) [h]	X	X	X	X		X							X	X	X		

Table 6.2: Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Continued)

Visit Description	Treatment and Evaluation															
CYCLE	Cycle 1				Cycle 2										Cycle 3 & Subsequent Cycles	EOT[a]	q3 mo F/U
Cycle Length (days)	21				21										21		
DAY	C1 D1	C1 D4	C1 D8	C1 D15	C2 D1								C2 D2	C2 D8	Cn D1		
Visit Window (days)		±1	±1	±1	±1									± 1	±2	+7	±30
HOUR					Pre-dose	0	1	2	4	6	8	10	24				
Lunch In Clinic[i]									X								
Gefitinib Administration In Clinic[h]	X	X	X	X		X							X	X	X		
Dinner In Clinic[h,i]												X					
DS 1205c Administration In Clinic (evening dose)[h]												X					
DS 1205a PK Blood Sample[j]	X[b,e]	X[b]	X[b]	X[b]	X[b]		X	X	X	X	X	X[b]	X[b]		X[b]		
Gefitinib PK Blood Sample[j]	X[b,k]	X[b]	X[b]	X[b]	X[b]		X	X	X	X	X	X	X[b]				
Exploratory Blood cfDNA Sample[l]	X[b]				X[b]										X[b] Day 1 of Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9...)	X	
Exploratory Blood Biomarker Sample[m]	X[b]	X[b]	X[b]	X[b]	X[b]										X[b] Day 1 of Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9...)	X	
Bone Scan[n]	X Every 24 weeks (±7 days)																
Tumor Assessment (CT/MRI)[o]	X[p] Every 6 weeks (±7 days) in the first 24 weeks after Day 1 of Cycle 1, and every 12 weeks (±7 days) thereafter															X[q]	
Chest Radiograph for Safety Examination	X Cycle 2 Day1 and Cycle 4 Day 1 (±2 days)																

Table 6.2: Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Continued)

Visit Description	Treatment and Evaluation															
CYCLE	**Cycle 1**				**Cycle 2**										**Cycle 3 & Subsequent Cycles**	**EOT[a]**	**q3 mo F/U**
Cycle Length (days)	**21**				**21**										**21**		
DAY	**C1 D1**	**C1 D4**	**C1 D8**	**C1 D15**	**C2 D1**								**C2 D2**	**C2 D8**	**Cn D1**		
Visit Window (days)		**±1**	**±1**	**±1**	**±1**									**± 1**	**±2**	**+7**	**±30**
HOUR					**Pre-dose**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**24**				
Ophthalmologic Assessments[r]					X										X Day 1 of Cycle 4 and every 4 cycles (7 days) thereafter	X	
ECHO/MUGA[s]					X										X Day 1 of Cycle 4 and every 4 cycles (7 days) thereafter	X	
New Cancer Treatment and Survival Follow up																	X
Tumor Biopsy (optional)				X[t]												X[u]	
Adverse Events[v]	←										X				→		
Prior/Concomitant Medications	←										X				→		

cfDNA cell free DNA; C cycle; CT computed tomography; D day; ECG electrocardiogram; ECHO echocardiography; ECOG Eastern Cooperative Oncology Group; EGFR epidermal growth factor receptor; EOT end of treatment; HIV human immunodeficiency virus; LVEF left ventricular ejection fraction; MRI magnetic resonance imaging; MUGA multigated acquisition scan; n number; PGx pharmacogenomics; PK pharmacokinetic(s); PS performance status; SpO_2 peripheral capillary oxygen saturation; T3 triiodothyronine; T4 thyroxine; TKI tyrosine kinase inhibitor; TSH thyroid stimulating hormone

a. This visit occurs within 7 days after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first. A follow up telephone call to the subject to review AEs/SAEs should occur 30 days (+7 days) after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first.
b. To be obtained/performed pre dose. All pre dose procedures should be obtained/performed prior to in clinic meal. As a general rule, blood collection should be conducted after ECG measurement. If blood collection need to be done before ECG measurement, investigators should contact Sponsor for guidance scheduling of these procedures.
c. May be performed Cycle 0, Day 7
d. Safety ECG recordings should be printed for on site safety assessment by the Investigator and submitted for central review. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point.
e. To be obtained/performed pre dose and at 2, 4, 6, and 8 hours post dose.

Table 6.2: Schedule of Events, Dose Escalation (Cycle 1 and Beyond) (Continued)

f. At every time point specified for 12 Lead Endpoint ECGs 3 Holter derived ECGs will be extracted by the central ECG laboratory. Subjects should rest supine for at least 10 minutes prior to and 5 minutes after each time point. When an ECG is performed at the same study time point as a PK sample, the PK sample should be taken immediately afterward. Refer to Investigator Site Manual for additional information.
g. Vital sign measurements include systolic/diastolic blood pressure and HR. Pulse oximetry should be performed with vital signs. Respiratory rate and body temperature should also be measured pre dose and at 2, 4, 6, and 8 hours post dose Cycle 1, Day 1 and pre dose Cycle 2, Day 1. Vital signs should be measured in the resting state. This procedure should not be conducted during the supine position for ECG measurement.
h. Beginning with Cycle 1, Day 1, DS 1205c should be administered following a meal, with 240 mL of water. On the morning of Endpoint ECG days, breakfast should be started 30 minutes prior to dosing and should be completed within approximately 20 minutes. For all other dosings, it is recommended that meals (breakfast or dinner) be completed within approximately 30 minutes; DS 1205c should be taken immediately after meal completion. Doses of DS 1205c should be taken approximately 12 hours apart. Gefitinib is co administered with the morning dose of DS 1205c. The Schedule of Events table above specifies only those meals and doses to be administered in clinic and does not explicitly list the meals and doses to be taken by the subject at home.
i. Meals administered in the clinic on Days 1, 4, 8, and 15 of Cycle 1 and Days 1 and 2 of Cycle 2 should be time matched to, and contain similar contents as meals administered on Day 1 of Cycle 0. Lunch can be given approximately 4 hours after dosing.
j. All PK blood draws should be performed as close as possible to the scheduled time, with windows of 2 hours (for pre dose), ±15 minutes(for hours 1 to 10 post dose), and ±2 hours (for 24 hours post dose). When an ECG is performed at the same time point, the PK specimen should be taken immediately after completion of the ECG. If both DS 1205a and gefitinib are measured at the same time point, separate 3 mL samples should be obtained. Refer to the Laboratory Manual for instructions about collection, processing, and shipping of samples.
k. To be obtained/performed pre dose and at 2, 4, 6, 8, and 24 hours post dose.
l. Obtain eight 5 mL samples for exploratory pharmacodynamic biomarkers (cfDNA and exosomes). As a general rule, blood collection should be conducted after ECG measurement. Refer to the Laboratory Manual for instructions for collection, processing, and shipping of samples.
m. Obtain three 3 mL samples for pharmacodynamic biomarkers (osteopontin, IL 8, sAXL) pre dose as indicated. As a general rule, blood collection should be conducted after ECG measurement. Refer to the Laboratory Manual for instructions for collection, processing, and shipping of samples.
n. A bone scan (99m technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F NaF) to assess bone metastases should be performed every 24 weeks (within that 24th week) from C1D1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan should be required at confirmation of CR to exclude new bone metastases. Lesions detected on bone scans must be followed with cross sectional imaging.
o. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments should be used throughout the study for all assessments for each subject unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1. Tumor assessments should be performed per RECIST version 1.1.
p. Investigator determined tumor assessments of the chest, abdomen, and pelvis and other areas where scans were performed at screening or newly suspected disease should be performed every 6 weeks (±7 days) from Cycle 1, Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter. Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Perform CT or MRI of the brain in subjects with baseline brain metastases or if clinically indicated, and within a target of 1 week after a subject achieves a CR.
q. Perform radiographic tumor assessments (CT/MRI) of the chest, abdomen and pelvis and all sites of disease, as per RECIST version 1.1. If the previous scan was performed within the last 6 weeks, this assessment does not need to be performed at the EOT visit.
r. Ophthalmologic assessments (visual acuity, slit lamp examination, fundoscopy, and tonometry) should be performed on Day 1 of Cycle 2 (7 days), on Day 1 of Cycle 4 (7 days) and every 4 cycles (7 days) thereafter, and at EOT(7 days). Investigators must ensure results of ophthalmologic assessments are available for review prior to dosing on corresponding cycle visits.
s. ECHO or MUGA should be performed on Cycle 2, Day 1 (7 days); Cycle 4, Day 1 (7 days), and on Day 1 of every 4 cycles (7 days) thereafter, and at EOT (7 days). The same test must be used for the subject throughout the study. Investigators must ensure results of ECHO/MUGA are available for review prior to dosing on corresponding cycle visits.

t. On study biopsy is optional on Cycle 1, Day 15 (+7 days). Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy may be obtained from primary tumor or metastatic site.
u. EOT tumor biopsy is optional. Tumor biopsy should be obtained from primary tumor or metastatic site, preferably from a site of recent radiographic progression, within 30 days of the last dose of study drug, and prior to starting any new anticancer treatment.
v. All clinical AEs occurring after the subject signs the Appropriate ICF and up to F/U visit (30 days [+7 days] after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first) should be reported.

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7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

7.1.1. Efficacy Endpoint(s)

Efficacy assessments will be determined at Screening and by follow-up imaging using RECIST version 1.1 (Section 17.2). Tumor assessments should be conducted every 6 weeks (±7 days) from Cycle 1, Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter, as indicated in the Schedule of Events (Table 6.2, Table 6.3), until radiological progression or until the subject permanently discontinues treatment. The schedule of efficacy assessments is determined relative to Cycle 1, Day 1 and will not be altered by interruptions in treatment. The antitumor activity endpoints will include percentage change in size of target lesion(s), ORR, DOR, DCR, PFS, and OS. ORR is defined as the sum of CR and PR rates. CR includes both confirmed CR (as described in Section 6.1.3.5 and Section 6.2.2.6) and unconfirmed CR. DOR is measured from the time of first CR or first PR until the first date of PD. TTR is measured from the date of first dose of DS-1205c to first objective response (CR or PR). DCR is the sum of CR rate, PR rate, and SD rate. PFS is defined as the time from the date of first dose of DS-1205c to the earliest date of the first objective documentation of radiographic disease progression per RECIST Version 1.1 or death due to any cause. OS is defined as from the date of first dose of DS-1205c to death due to any cause.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

Blood samples for PK analyses of DS-1205a and gefitinib should be obtained at the time points specified in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). Sampling time points may be modified based on available data from PK analyses during the study. At each time point, a 3-mL blood sample will be collected for DS-1205a and/or gefitinib analysis. If both DS-1205a and gefitinib are measured at the same time point, separate 3-mL samples should be obtained. Instructions for the collection, handling, storing and shipping of the PK samples for DS-1205a and gefitinib PK analyses will be included in the Laboratory Manual. The actual date and exact time of study drug administration and of blood sampling for DS-1205a and gefitinib PK analysis must be recorded on the eCRF.

All PK samples should be taken at as the exact nominal time point as possible. If time points of PK sampling coincide with those of Safety or Endpoint ECG, PK samples should be taken immediately after ECG measurement.

Plasma concentrations of study drugs will be measured using validated assays at Sponsor-designated bioanalytical laboratories. The samples may be used for bioanalytical method development and validation. The leftover PK samples after bioanalysis will be used for metabolite profiling, and the results will be reported separately.

Plasma concentrations will be used to determine the following PK parameters using the actual sample collection times and the standard non-compartmental analysis (NCA).

- Cmax, Tmax, Ctrough, AUCtau, and other PK parameters as appropriate.

8.2. Biomarkers

Biomarker analyses will be used to investigate the effect of DS-1205c and DS-1205c in combination with gefitinib at the molecular and cellular levels as well as to determine how changes in the markers may relate to exposure and clinical outcomes. The sample collection information as required should be recorded in the eCRF and laboratory requisition form(s). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

8.2.1. Pharmacodynamic Biomarker Assessments in Blood Samples

Pharmacodynamic biomarkers will be analyzed with the intent of monitoring the antitumor impact of treatment with DS-1205c and DS-1205c in combination with gefitinib as exploratory investigations. The following exploratory pharmacodynamic biomarkers that may be measured may include but are not limited to are osteopontin, IL-8, sAXL, cfDNA, and the composition of exosomes. These biomarkers will be measured at specified times in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). Other pharmacodynamic biomarkers in addition to, or in place of, these may be considered as suggested by new scientific findings, and may include DNA, RNA, protein or other

molecules. One or more of the aforementioned pharmacodynamic biomarkers may also be explored for predictive value.

Plasma samples for biomarker analysis will also be tested for the presence of EGFR mutations known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) and resistance (T790M) using the cobas® EGFR Mutation Test v2.

Sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

8.2.2. Biomarker Assessments in Tumor Tissue Samples

Fresh biopsy tissue or an archived tumor specimen will be obtained prior to enrollment to assess the baseline expression of biomarkers which may relate to response to DS-1205c in combination with gefitinib. Tumor specimens will be used to assess AXL expression using IHC and mRNA. In addition, the mRNA analysis of several hundred genes, including AXL and AXL pathway genes will be measured using NanoString technology and/or other methods (such as next-generation DNA sequencing [NGS] or protein analysis). Additional markers or methods may be utilized for testing these samples.

8.2.2.1. Tumor Biopsy Sample Collection

Study Entry

All subjects will be asked to provide consent to supply tumor tissue (archival tissue or fresh tumor biopsy) after progression during treatment prior to study entry.

- Archival tumor tissue may be provided for analysis if:

  tissue has been obtained after progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib, AND

  the tissue biopsy was obtained within 6 months of the date of consent, AND

  sufficient quantity is available

- Fresh Tumor Tissue Collection

  In the event that a subject does not have adequate tumor tissue as required per the Laboratory Manual, a fresh tumor biopsy should be obtained.

  A fresh tumor biopsy should be obtained from a primary tumor or metastatic site, not previously irradiated, and preferably from a site of disease progression.

On-Study Biopsy

- An optional On-Study tumor biopsy may also be performed on Cycle 1, Day 15 (+7 days). Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy should be obtained from primary tumor or metastatic site. CBC must be obtained within 2 days of the

tumor biopsy and results must be reviewed by the Investigator prior to obtaining a tumor biopsy.

EOT Biopsy

- An optional EOT tumor biopsy will also be performed at the time of progression or discontinuation from study treatment. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy should be obtained from primary tumor or metastatic site, preferably from a site of recent radiographic progression, within 30 days of the last dose of study drug, and prior to starting any new anticancer treatment.

Refer to the Laboratory Manual for instructions regarding archived and fresh tumor tissue requirements and shipping.

8.2.2.1.1. Epidermal Growth Factor Receptor (EGFR) T790M

All subjects will be required to provide tumor tissue from a biopsy performed since progression during treatment with gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib.

Subjects are required to demonstrate an absence of EGFR T790M mutation prior to study entry, assessed in tumor tissue using either cobas® EGFR Mutation Test v2 or gene panel testing (FoundationOne CDx™ or OncoGuide™ NCC Oncopanel System) performed locally at a CAP or an ISO15189 certified laboratory.

8.2.2.2. Tumor Tissue Biomarker Analysis

Tumor tissue from Screening (fresh tumor biopsy or archived tumor specimen) and from the optional EOT biopsy will be used to assess for the presence of EGFR mutations known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) and resistance (T790M) using the cobas® EGFR Mutation Test v2. Also, exploratory biomarker analysis, including, but not limited to, AXL (or other protein) expression using IHC, mRNA of several hundred genes (including AXL and AXL pathway genes), will be measured using NanoString technology, as well as possibly testing for mutations in DNA and/or other methods. Additional samples may be requested if the original sample is of insufficient quantity or quality to complete planned analyses. These results are not required for study entry.

8.2.3. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, exploratory research may be conducted on any tumor or blood sample. These studies would extend the search for other potential biomarkers relevant to the effects of DS-1205c and DS-1205c in combination with gefitinib, cancer and/or the resistance to the treatment. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, and availability of reagents and samples.

If the patient agrees, the remaining biomarker samples (tumor) may be stored for up to 15 years, depending on local regulations, and further analyzed to address scientific questions related to DS-1205c and/or cancer. This may include the development of methods to treat, monitor, or detect cancer. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

At the end of the storage period, or during the storage period, if the subject withdraws consent, blood and tissue samples of the subject will be promptly managed regarding proper disposition. However, the data will not be discarded if biomarker analysis has been completed before the subject withdraws consent.

If the patient refuses consent to provide blood sample before the enrollment, the subject will not be enrolled to the study. If the patient refuses consent to provide tumor sample which is corrected for the screening assessment before the enrollment, the subject will not be enrolled to the study. If the patient refuses consent to provide optional tumor samples which is corrected after the treatment of study drug before the enrollment, the subject will be able to be enrolled.

8.2.4. Disclosure of the Results of Biomarker Assessment

The tissue screening results of EGFR mutation will be disclosed to the subject or investigators as they affect the treatment selection. Because the value of future additional biomarker assessments is unknown at this time, any individual results obtained from exploratory biomarker research will not be disclosed to the subject or investigators.

8.3. Pharmacogenomic Analysis

8.3.1. Study Subjects for Pharmacogenomic Analysis

Pharmacogenomic samples will be collected from subjects who have given informed consent for pharmacogenomic testing as part of the main study ICF. For subjects who give informed consent for pharmacogenomic analysis, the Investigator will record the date of that consent in the eCRF.

8.3.2. Collection of Specimens for Pharmacogenomic Analysis

A single 10-mL blood sample for pharmacogenomic analysis will be collected from each subject who has provided informed consent, according to the Schedule of Events (Table 6.1, Table 6.3). Sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

8.3.2.1. Pharmacogenomic Endpoints

Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of DS-1205c. Additionally, samples may be analyzed for genes involved in DS-1205c-related signaling pathways, or to examine diseases or physiologic processes related to DS-1205c action. Subject specimens will not be sold to anyone. This information may be useful in identifying

genetic differences among individuals that explain variations in response to the study drug or elucidating whether such genetic differences are present in germline DNA or whether they arise by somatic mutation.

8.3.2.2. Disclosure of the Results of Pharmacogenomic Analysis

Because the nature and value of future pharmacogenomic research cannot be known at this time, any results obtained from research involving pharmacogenomic samples will not be disclosed to the subject or Investigators now or in the future.

8.3.2.3. Storage and Disposal of Specimens for Pharmacogenomic Analysis

Samples will be retained until exhausted, or for up to 15 years if required by local regulations, or until the Sponsor requests disposition.

If the subject withdraws consent, the banked blood samples will be promptly managed regarding proper disposition. However, the data will not be discarded if pharmacogenomic analysis has been completed before the subject withdraws consent.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Events

All clinical AEs (see Section 9.4 for definitions) occurring after the subject signs the Appropriate ICF and up to F/U visit (30 days [+7 days] after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first) after the last dose of study drug, whether observed by the Investigator or reported by the subject, will be recorded on the eCRF. In addition, any SAEs directly related to tumor biopsy after the subject signs the appropriate ICF should be reported according to Section 9.5. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to signing the appropriate ICF will be recorded as part of medical history.

All AEs, SAEs, and adverse events of special interest (AESIs) are to be reported according to the procedures in Section 9.5.

All clinical laboratory results, vital signs, and safety ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently, should not be reported as an AE or SAE. However, when a subject dies from disease progression with no other underlying or immediate causes, "disease progression" should be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

9.2. Safety Endpoints

Safety endpoints will include SAEs, TEAEs, DLTs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the NCI-CTCAE version 5.0.

9.3. Adverse Events of Special Interest (AESI)

The following AESIs should be reported to the Sponsor by the Investigator in electronic data capture (EDC) within 24 hours of awareness.

9.3.1. Elevations of Aminotransferase(s) and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST ≥ 3.0 × ULN with simultaneous total bilirubin [TBL] ≥ 2.0 × ULN) should always be reported to the Sponsor using a special collection eCRF, with the Investigator's assessment of seriousness, causality, and a detailed narrative.

If the subject discontinues the study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations in order to determine the nature and severity of the potential liver injury.

9.3.2. Prolonged QTc Interval（≥ Grade 2）

Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. Safety ECGs will be reviewed and interpreted on-site by the Investigator and evaluated by central reviewer. QTc prolongation more than Grade 2（average QTc 481 - 500 ms）should be reported as a AESI. For more information regarding collection of ECGs, refer to Section 9.10.

If a subject experiences QTc prolongation of Grade 4 (torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), then the subject should be discontinued from study treatment.

9.3.3. Interstitial Lung Disease

Lung disorders, including interstitial lung disease (ILD), are acknowledged in the current reference safety information for gefitinib (see current prescribing information). If a subject is suspected or diagnosed as having ILD, the Investigator should consult with a

pulmonologist as needed, and the subject will be treated appropriately. The study treatments will be interrupted until drug induced pulmonary toxicity can be ruled out. Study treatments will be permanently discontinued upon confirmation of drug-induced ILD or pneumonitis. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. See Section 9.12 for details regarding pulmonary assessments.

9.4. Definitions

9.4.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

9.4.2. Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Adverse Event Severity

The severity of AEs will be graded using the NCI-CTCAE v5.0. For each episode, the highest severity Grade attained should be reported.

The NCI-CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI-CTCAE guidelines should be followed closely.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE Grade may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the Investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation, that immediately makes the event serious based upon hospitalization without regard to the Investigator assessment of severity.

9.4.4. Causality Assessment

The Investigator should assess the causal relationship between an AE and the study drugs on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:

  The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject’s

clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications), or

The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

- Not Related:

  The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made
- Drug Withdrawn: The study drug was permanently stopped
- Dose Reduced: The dosage of study drug was reduced
- Drug Interrupted: The study drug was temporarily stopped
- Not applicable

9.4.6. Other Action Taken for Event

- None: No treatment was required
- Medication required: Prescription and/or over-the-counter (OTC) medication was required to treat the AE
- Hospitalization
- Other

9.4.7. Adverse Event Outcome

- Recovered/Resolved: The subject fully recovered from the AE with no residual effect observed
- Recovering/Resolving: The AE improved but has not fully resolved
- Recovered/Resolved with Sequelae: The residual effects of the AE are still present and observable
- Not Recovered/Not Resolved: The AE itself is still present and observable
- Fatal should be used when death is a direct outcome of the AE
- Unknown

9.5. Serious Adverse Events Reporting Procedure For Investigators

All AEs, AESIs, and SAEs will be reported in the eCRF.

Serious events that are also efficacy endpoints (disease progression) will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE and captured in the designated eCRF. These events are clinically anticipated events in the target treatment population, and will be periodically reviewed to ensure prompt identification of any clinically concerning safety issues.

The following types of events should be reported by the Investigator in electronic data capture (EDC) within 24 hours of awareness. In the event that eCRF is unavailable, report the folloing types of events by faxing the paper Serious Adverse Event Report (SAVER) Form to the CRO using the provided fax transmittal form and the appropriate fax number provided for your country. Please enter SAEs reported on the paper SAVER Form into the eCRF as soon as possible. Please refer to eCRF Completion Guide for additional instructions.

- SAEs (see Section 9.4.2 for definition)
- Hepatic events (both serious, non-serious, and clinical laboratory results) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥ 3 x ULN with simultaneously elevated total bilirubin > 2 x ULN should be reported as an AE/AESI (see Section 9.3.1 for details) regardless if these hepatic events are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, constitute an AE in the Investigator's clinical judgment, or are related to disease progression.
- AESIs: interstitial lung disease (Section 9.3.3) and prolonged QTc interval (≥ Grade 2) (Section 9.3.2)

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Institutional Ethics Committee

The Sponsor and/or CRO will inform Investigators, IRBs/IECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other

study sites or other studies of the investigational drug, as appropriate per local reporting requirements. The Sponsor and/or CRO will comply with any additional local safety reporting requirements.

In Japan, it is the Sponsor's responsibility to report all the fatal/life-threatening adverse reactions to the regulatory authorities regardless of expectedness, and SUSARs to the regulatory authorities and IRB/IECs.

9.7. Exposure In Utero During Clinical Studies

The Sponsor must be notified of any subject who becomes pregnant while receiving, or within 3 months of discontinuing, the study drug. Sponsor. must be notified of any male subject whose female partner becomes pregnant while the subject is receiving, or within 3 months of discontinuing, the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used.

Clinical laboratory results will be entered in the eCRF, including whether measurements were obtained, date of measurement, and results of measurements.

Standard clinical laboratory tests listed in Table 9.1 should be performed per the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3).

At Screening, creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.1).

In addition, a serum pregnancy test (beta hCG) will be required for all female subjects of childbearing potential at Screening. Urine pregnancy tests will be performed throughout the remainder of the protocol per the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). A positive urine pregnancy test result must be confirmed immediately using a serum test.

Table 9.1: Clinical Laboratory Tests

Laboratory Tests	Parameters
Hematology	Red blood cell count, Hb, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	Total protein, albumin, ALP, ALT, AST, TBL, BUN, calcium, chloride, CK, serum creatinine, lipase, LDH, magnesium, potassium, sodium, FSH (if indicated), estradiol (if indicated), T3[FT3][a], TSH[a], T4[FT4][a], triglycerides, serum amylase
Coagulation	PT-INR, and aPTT
Urinalysis	Protein, glucose, blood, microscopy assessments (if indicated), and specific gravity

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; FSH = follicle-stimulating hormone; PT-INR = prothrombin time–international normalized ratio; T3 = triiodothyronine; FT3 = free triiodothyronine; T4 = thyroxine; FT4 = free thyroxine; TBL = total bilirubin; TSH = thyroid stimulating hormone

[a] Thyroid function tests (ie, T3[FT3], T4[FT4], and TSH) will be performed as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). More frequent examinations may be performed at the discretion of the Investigator and if indicated.

All clinical laboratory values must be assessed by the Investigator as to clinical significance and used to direct appropriate clinical management measures. All abnormal clinical laboratory values considered clinically significant by the Investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, eCRF should be submitted and other relevant procedures must be followed (see Section 9.5). Abnormal clinical laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure and HR, respiratory rate, and body temperature. Additionally, pulse oximetry (SpO_2) will be performed as outlined in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3).

Blood pressure and HR will be measured in the resting state.

This procedure should not be conducted during the supine position for ECG measurement.

9.10. Electrocardiograms

9.10.1. Safety ECGs

The corrected QT intervals using Fridericia's formula will be used for clinical assessments and should be calculated as follows:

$$\mathrm{QTcF} = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}$$

Electrocardiograms will be performed in triplicate at baseline during Screening and evaluated by a central laboratory. Triplicate ECGs (approximately 1 minute apart) will be obtained after the subject has rested supine for at least 10 minutes. The mean QTcF of the triplicate set of ECGs will be used to determine eligibility.

12-lead ECGs will be performed at specified time points as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). At each time point, the subject will be resting in a supine position for at least 10 minutes prior and 5 minutes after the specified times. When vital sign assessments, Safety ECGs, Endpoint ECGs, and blood sampling coincide, procedures should be carried out in said order.

Safety ECGs should be printed for each specified time point and evaluated by the Investigator on-site. Safety ECGs will also be submitted to the central laboratory. Other unscheduled ECGs may be performed as clinically indicated.

Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. Please refer to the Investigator Site Manual for additional information on the collection of ECGs.

If a subject experiences QTc prolongation of Grade 4 (torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), then the subject should be discontinued from study treatment.

9.11. Physical Examinations

Physical examinations will include evaluation of the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological.

9.12. Other Examinations

Left Ventricular Ejection Fraction (LVEF):

- LVEF will be measured by either ECHO or MUGA, as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). All ECHO/MUGA assessments must be evaluated by the Investigator or delegate. The same modality (ECHO or MUGA) should be used for the subject throughout the study.
- Refer to Section 17.3 for NYHA Functional Capacity and Objective Assessment.

Ophthalmologic Assessments:

- Ophthalmologic assessments will include visual acuity testing, slit lamp examination, fundoscopy, and tonometry as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). All ophthalmologic assessments

must be evaluated by the Investigator or delegate. More frequent examinations may be performed at the discretion of the Investigator and if indicated. A 30-day follow-up assessment is required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

Pulmonary Assessments:

- SpO_2, will be performed as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). Additional testing to investigate pulmonary disorders may be performed, eg, chest radiograph, functional/blood-gas examination, pulmonary function testing, or serological examinations, at the Investigator's discretion as described in Table 5.1. An ILD Adjudication Committee (AC) will be set up for this study. Additional details regarding the ILD AC are available in Section 11.6.6.

Neurologic Assessments:

- In a subject who develops new or progressive neurologic symptoms, such as peripheral neuropathy NCI-CTCAE Grade 3 to 4, delay dose and subject should be monitor at least twice a week until resolved to NCI-CTCAE ≤ Grade 1. Unscheduled imaging of the brain or spinal cord may also be conducted to evaluate subjects with neurologic symptoms.

Thyroid Assessments:

- Hypothyroidism has been associated with several TKIs (eg, sunitinib and sorafenib), with increases in thyroid stimulating hormone (TSH) reported.[41] Although an association with gefitinib has yet to be established, thyroid function tests (ie, T3[FT3], T4[FT4], and TSH) will be performed as described in the Schedule of Events (Table 6.1, Table 6.2, and Table 6.3). More frequent examinations may be performed at the discretion of the Investigator and if indicated.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

Descriptive statistics will be provided for selected demographic, safety, PK, and biomarker data from both Dose Escalation and Dose Expansion by dose level within each part and visit as appropriate. Descriptive statistics for continuous data will include means, medians, standard deviations, and minimum and maximum , while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. Time-matched baseline will be derived from Cycle 0, Day -1 measurements for all ECG.

Safety analyses will be performed based on the safety analysis sets. Analysis of PK parameters will be based on the PK analysis sets, and biomarker analyses will be based on the PD biomarker analysis sets.

Efficacy endpoints will be analyzed based on the Full Analysis Set (FAS). Data from Dose Escalation will be summarized by dose level within each part and overall.

A detailed statistical analysis plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized before database lock. Statistical methods described within may be changed based on advances in research.

11.2. Analysis Sets

- Enrolled Analysis Set will include all subjects who sign the ICF of the study.
- FAS will include all subjects in the Enrolled Analysis Set who received at least one dose of DS-1205c and who had baseline and post-treatment evaluable tumor assessments.
- DLT-Evaluable Set will include subjects enrolled in Dose Escalation who had at least one DLT during the 7 days of Cycle 0 or the 21 days of Cycle 1, or did not have a DLT but received at least 75% of the doses in the 21 days of Cycle 1.
- Safety Analysis Set will include all subjects in the Enrolled Analysis Set, who received at least one dose of DS-1205c. Four groups of subjects will be identified within the Safety Analysis Set: (1) subjects in Dose Escalation, (2) subjects in Dose Expansion, (3) subjects treated at the dose level of RDE, and (4) all treated subjects in the study.
- PK Analysis Set will include all subjects in the Enrolled Analysis Set who received any amount of the study drugs and have sufficient plasma concentration data to characterize PK of DS-1205a or gefitinib.

- Concentration-QTc Analysis Set will include all subjects who are in the Safety Analysis Set with at least one pair of postdose plasma concentration data and QTc data from the same timepoint. The concentration-QTc Analysis Set will be used for the concentration-QTc analysis.
- Biomarker Analysis Set will include all subjects in the Enrolled Analysis Set who received any amount of study drugs and who had the baseline tissue biopsy assessment and, where applicable, at least 1 post-treatment blood sample assessment for biomarkers.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the Enrolled Analysis Set.

Demographic and baseline characteristics such as age, sex, race, histology, cancer status (metastatic and/or unresectable), molecular mutations (if available), prior treatment regimen(s), best response to prior anticancer treatment(s), will be summarized for the Enrolled Analysis Set, FAS, and Safety Analysis Set. If 2 analysis sets within a part of the study are identical to each other, the table will be presented only once.

Study drug exposure, treatment duration, and compliance with study therapy will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Efficacy Analyses

Final data analysis for the clinical study report will occur at the end of the study when all subjects have either completed the End-of-Study Follow-up or discontinued from the study or have received at least 6 months of therapy.

Efficacy endpoints will include ORR (the number of subjects with best objective response [CR or PR], divided by the number of subjects in the analysis population), DOR, DCR (the sum of CR rate, PR rate, and SD rate), TTR, PFS, and OS. CR includes both confirmed CR and unconfirmed CR. Tumor responses will be assessed by an Investigator according to RECIST version 1.1 (Section 17.2).

The efficacy endpoints will be listed and summarized using descriptive statistics based on the FAS by dose level within each part and overall. Study data will be analyzed and reported based on all subjects' data from Dose Escalation and Dose Expansion up until the time when all subjects have potentially completed at least 6 cycles of treatment. Analyses will be performed for each dose level.

The ORR will be based on Investigator's assessments. The analysis will be based on subjects dosed at the level of RDE at both the dose escalation part and the dose expansion part. Subjects with unknown or missing response will be treated as non-responders. Point estimates and 2-sided 95% exact binomial confidence intervals (CIs) will be provided

DOR (the time from documentation of tumor response [either CR or PR] to disease progression) will be based on Investigator's assessments. The DOR will be summarized with median event times with 2-sided 95% CI using the Kaplan-Meier method.

DCR will be reported as a summary statistic by dose cohort. Point estimates and 2-sided 95% exact binomial CIs will be provided.

Time-to-event variables including PFS, TTR, and OS will be summarized with median event times with 2-sided 95% CI using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the time to event endpoints such as PFS analysis will be specified in the SAP.

Descriptive statistics for the best percentage change from baseline in the sum diameters of measurable tumors will be provided. A waterfall plot of the best percentage change in the sum of diameter for each subject will be presented. In addition, sensitivity analyses will be performed to include confirmed CR only.

11.5. Pharmacokinetic Analyses

PK parameters for each subject will be estimated using non-compartmental analysis (NCA). Descriptive statistics will be provided for all plasma concentration data by analyte/dose/study day/time and for each PK parameter by analyte/dose/study day, as appropriate.

11.6. Safety Analyses

Safety endpoints will include AEs, clinical laboratory measurements, vital sign measurements, ECG recordings, physical examination findings, ECHO/MUGA findings, and ophthalmologic findings. AEs and abnormal laboratory values will be graded according to the NCI-CTCAE version 5.0.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In Dose Escalation, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized by dose level.

11.6.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period (from first DS-1205c/gefitinib dose date until follow-up call [Section 6.1.3.9 or Section 6.2.2.10] after the last dose of study medication), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline, but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the AE is continuous.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE Grade, System Organ Class (SOC), and Preferred Term (PT).

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to DS-1205c or gefitinib.

A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, PT, SOC, NCI-CTCAE Grade, and relationship to study medications.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from study treatment, will be listed.

AESIs will be added as needed. The details will be described in the SAP.

11.6.2. Electrocardiogram Analyses

Electrocardiogram parameters (PR, RR, QRS, QT, and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation, including the EOT visit and the maximum post-treatment value. The corrected QT intervals using Fridericia's formula will be calculated as follows: QTcF QT/$(RR)^{1/3}$.

The incidence of notable ECG changes in maximum absolute QT and QTcF intervals over all post-treatment evaluations, as well as in QT and QTcF maximum changes from baseline over all post-treatment evaluations will be summarized. A listing of ECG data will be provided.

The Concentration-QTc analysis plan will be presented in a separate document.

11.6.3. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results (hematology, blood chemistry, coagulation, and urinalysis) by scheduled time of evaluation and by treatment group using the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the EOT visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE v5.0, if applicable, and the Grade will be presented in a by-subject data listing. A shift table, presenting by treatment group the two-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE Grade will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.6.4. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and using the Safety Evaluation Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment.

11.6.5. Physical Examination Analyses

A listing of physical examination findings will be provided for the Safety Analysis Set.

11.6.6. Interstitial Lung Disease Analysis and Adjudication

An external ILD AC will be established for this study. Details on the membership, responsibilities, and working procedures of the external ILD AC will be described in its

own charter, provided as a separate document in the study file. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for ILD adjudication, these additional data collections will cover a more in-depth medical history (eg smoking, radiation, COPD and other chronic lung conditions, etc), diagnostic evaluation, treatment and outcome of the event. The data collection will be triggered for any safety event reported using a Medical Dictionary for Regulatory Activities (MedDRA) PT from the current ILD standardized MedDRA query (SMQ)

The ILD AC will adjudicate ILD cases (including potential ILD) on an ongoing basis. Adjudication of ILD cases will be based on evaluation of eCRFs and source documents including but not limited to chest high-resolution CT, arterial blood gases, and diffusing capacity of lung carbon monoxide (DLCO). The ILD AC will review ongoing cases of ILD to make the final determination of ILD diagnoses to guide Sponsor decisions regarding trial suspension or trial discontinuation and to provide assessment of ILD prevalence at the end of study. Findings of the ILD AC with its recommendations will be provided to the Sponsor.

11.7. Interim Analyses

No formal interim analysis is planned, except for the assessment of the RDE.

11.8. Data Monitoring Committee

Not applicable.

11.9. Sample Size Determination

Phase 1 dose escalation : ≥ 18 subjects

The Dose Escalation part of this study consists of mCRM with EWOC design with at least 3 DLT-evaluable subjects per dose level. At least 18 DLT-evaluable subjects are needed to reach an accurate estimate of the maximum tolerated dose (MTD). There will be at least 18 DLT-evaluable subjects treated to reach an accurate estimate of the RDE in Dose Escalation, with at least 6 subjects treated at the final selected dose.

11.10. Statistical Analysis Process

The clinical study will be analyzed by the Sponsor.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, North Carolina 27513).

11.11. Specification of Modified Continuous Reassessment Method with Escalation With Overdose Control

In this study mCRM will be based on a 2-parameter BLRM, as defined below.

11.11.1. Bayesian Logistic Regression Model for Modified Continuous Reassessment Method

The dose-toxicity relationship for mCRM with EWOC principle will be described by a 2-parameter BLRM:

$$\text{logit}(\pi(d)) \quad \log(\alpha) + \beta \log(d/d^*), \qquad \alpha > 0, \beta > 0$$

where $\text{logit}(\pi(d)) \quad \ln(\pi(d)/(1-\pi[d])$, and $\pi(d)$ is the probability of a DLT or DLT rate at dose d. Doses are rescaled as d/d^* with the reference dose $d^* \quad 800$ mg. As a consequence, α is equal to the odds of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

11.11.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior for the model parameters $(\log(\alpha),\log(\beta))$ is obtained as follows:

- The best guess of the MTD is projected to be around 800 mg in humans. The median prior probabilities of DLT are set to be approximately 8% and 24.5% at 200 mg (projected starting dose for dose escalation using mCRM) and the projected MTD of 800 mg, respectively.
- For the remaining doses, the prior medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative Beta distributions), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard Deviations	Correlation
log(α), log(β)	(−1.1493, −0.5514)	(2.0739, 1.5228)	−0.1943

11.11.3. Escalation With Overdose Control Principle

Dose recommendation for the next cohort of patients will be based on summaries of the posterior probability of DLT rate for provisional doses.[44] After each cohort of subjects completes DLT evaluation during Cycle 1, the joint posterior distribution of the BLRM parameters will be generated according to the Bayes' theorem based on the likelihood function of the accumulated DLT data from Cycle 1 and the prior distribution. Posterior probabilities of DLT rate at different dose levels will then be obtained from updated BLRM, and summarized for DTL rate in 4 different ranges: under-dosing (ie, DLT rate within [0, 0.16]), target toxicity (ie, DLT rate within [0.16, 0.33]), excessive toxicity (ie, DLT rate within [0.33, 0.60]), and unacceptable toxicity (ie, DLT rate within [0.60, 1.00]). The dose level recommended by mCRM for dosing next cohort will be based on these probabilities according to the EWOC principle. The EWOC principle requires that the mCRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate range of [0.16, 0.33] among all doses fulfilling the overdose control constraint that there is less than 0.25 of probability for DLT rate > 0.33 (probability for excessive or unacceptable toxicity).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/study site will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The Sponsor, CRO monitor, and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF.

All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an EDC "audit trail."

The eCRF completion should be kept current to enable the study monitor to review the subject's status throughout the course of the study. eCRFs will be completed, reviewed

and signed off or e-signed by the Investigator as described in the Data Management Plan and in the monitoring plan for Clinical Research Associates.

Upon completion of the subject's eCRF, it will be reviewed and signed off by the Investigator via the EDC system's electronic signature. This signature will indicate that the Investigator inspected or reviewed the data in the eCRF, the data queries, and the site notifications and agrees with the eCRF content.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data. Data will be vetted both electronically and manually for eCRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using the latest version of the MedDRA.

All concomitant medications and prior cancer therapies will be coded using the latest version of the World Health Organization Drug Dictionary (WHODRUG).

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date, and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential SID number list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, informed consents, and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/IEC and Sponsor
- Records related to the study drug(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

12.5. Record Keeping

Records of subjects, source documents, data correction forms, eCRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/IEC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

All study related essential documentation will be retained by the Investigator until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have lapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Sponsor or a CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. Sponsor follows the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure that Sponsor is in compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the Sponsor prior to submission.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s), including the following:

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312 as appropriate
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997.
- Other applicable local regulations

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB/IEC prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

The consent for screening tumor tissue collection (archival or fresh tumor biopsy) should be documented in the tissue consent form.

Consent for PGx sampling for banking, the on-study biopsy, and the post-treatment tumor biopsy should be documented in the main study consent form. Participation for PGx sampling for banking, the on-study biopsy, and the post-treatment tumor biopsy are each optional for all subjects. Those subjects who choose not to provide a sample for PGx sampling for banking or not to provide the post-treatment tumor biopsy may still participate in the main portion of the study.

For studies in the US, an additional consent will be required for the Health Insurance Portability and Accountability Act. Subjects are free to withdraw from the study at any time, without prejudice to further treatment.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IRB/IEC for ethical review and approval according to local regulations, prior to the study initiation. The written approval should identify all documents reviewed by name and version.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made,

this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable regulatory authority(-ies) in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(-ies), and which was given approval/favorable opinion by the IRBs/IECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, IRBs/IECs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/IEC. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant

information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that are deemed necessary as the study progresses will be communicated to the Investigator by the Sponsor or the CRO. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. The Sponsor will assure the timely submission of amendments to regulatory authorities in accordance with the governing regulations.

Changes made by protocol amendments will be documented in a Summary of Changes document.

15.8. Study Termination

The Sponsor has the right to terminate the study at any time and study termination may also be requested by (a) competent authority(-ies).

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and regularly updated as necessary.

15.10.1. Sponsor

Japan
Daiichi Sankyo Company, Limited
3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan

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17. APPENDICES

17.1. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation[45] based on actual weight in kilograms (1 kilogram 2.2 pounds):

Conventional (serum creatinine in mg/dL):

Male:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) (serum creatinine in µmol/L):

Male:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

17.2. Response Evaluation Criteria in Solid Tumors, Version 1.1

Assessment of tumor responses will be performed according to revised RECIST guidelines, Version 1.1.[46] Some of these definitions and criteria are highlighted below.

17.2.1. Measurability of Tumor at Baseline

17.2.1.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

17.2.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

  10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

  10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

  20 mm by chest X-ray

- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on “Baseline documentation of target and non-target lesions” for information on lymph node measurement.

17.2.1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

17.2.1.1.3. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

17.2.1.1.3.1. Bone Lesions

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

17.2.1.1.3.2. Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.2.1.1.3.3. Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

17.2.1.2. Specifications by Methods of Measurements

17.2.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 22 days (Dose Escalation) or 30 days (Dose Expansion) before the first dose of study drug administration.

17.2.1.2.2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

17.2.2. Tumor Response Evaluation

17.2.2.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Only subjects with measurable disease at baseline should be included in the study.

17.2.2.2. Baseline Documentation of "Target" and "Non-target" Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (representative of all involved organs) should be identified as target lesions and

will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.” In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

17.2.2.3. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

17.2.2.3.1. Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase

of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

17.2.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

17.2.2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of 1 or more new lesions is also considered progression).

17.2.2.3.4. Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in "volume" [which is equivalent to a 20% increase diameter in a measurable lesion]). If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so: therefore, the increase must be substantial.

17.2.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on an F/U study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and F/U evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

17.2.2.4. Evaluation of Best Overall Response

17.2.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 17.1: Overall Response: Subjects with Target (±Non-target) Disease

Time Point Response: Subjects with Target (±Non-target) Disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

17.2.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular time point, the subject is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at F/U only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

17.2.2.4.3. Best Overall Response: All Time Points

Best response determination in trials where confirmation of CR or PR is required: When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline, 6 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Table 17.2.

Table 17.2: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response, First Time Point	Overall Response, Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD (6 weeks) was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

17.2.2.4.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an

objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

17.2.2.4.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to F/U. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 22 days of the first dose of study drug administration.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the brain, chest, abdomen, and pelvis at screening period. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur during study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during study period. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

17.3. New York Heart Association Functional Capacity and Objective Assessment

The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 14, 1994. The new classifications are summarized below for the many physicians and scientists who use them to describe the status of individual patients.

Table 17.3: New York Heart Association Functional Capacity and Objective Assessment[47]

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

17.4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Table 17.4: Eastern Cooperative Oncology Group Performance Status Scale[48]

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

17.5. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0[49]

1. Toxicity Grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 different criteria grades might be applicable for rating a particular toxicity, or similar toxicities, the more severe Grade should be used.
3. Any toxicity resulting in death is defined as Grade 5.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. The NCI-CTCAE v5.0 is accessible online at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

17.6. QT-Prolonging Medications and CYP3A4 Inhibitors/Inducers

Lists of medications that potentially prolong QT/QTc and medications and foods that are common inhibitors/inducers of CYP3A4 are provided as supplements. Those lists should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to prolong QT/QTc and/or inhibit/induce CYP3A4.