CLINICAL STUDY PROTOCOL

A Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer

Protocol Number CT-P16 3.1

EudraCT Number 2018-002147-28

Sponsor:

CELLTRION, Inc.
23, Academy-ro,
Yeonsu-gu, Incheon, 22014, Republic of Korea
Phone: +82 32 850 5000
Fax: +82 32 850 5050
E-mail: contact@celltrion.com

[redacted]

Version and Date of Protocol: Protocol Version 2.0, 14 June 2019

CONFIDENTIAL

Protocol Approval

Study Title	A Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer
Protocol Number	CT-P16 3.1
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Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.0, dated 14 June 2019, the International Council for Harmonisation harmonized tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number: CT-P16 3.1
Title: A Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer
Study Phase: Phase 3
Study Centers: It is expected that approximately 150 study centers will participate in the study.
Test Drug, Dose and Regimen: During the Induction Study Period, 15 mg/kg intravenous (IV) of CT-P16 will be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles. Paclitaxel 200 mg/m^2 IV and carboplatin area under the curve (AUC) 6 IV also will be administered on Day 1 of each cycle and will be repeated every 3 weeks up to 6 cycles (at least 4 cycles). After the Induction Study Period, CT-P16 as a monotherapy will be maintained every 3 weeks until progressive disease (PD) or intolerable toxicity occurrence. Dose reduction of CT-P16 for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. CT-P16 will be diluted in a total volume of 100 mL of 0.9% sodium chloride and administered by IV infusion with an infusion pump. The dose should be delivered over 90 minutes (±15 minutes) at the Cycle 1 of the Induction Study Period. If the infusion is well-tolerated, the infusion of the Cycle 2 of the Induction Study Period may be administered over 60 minutes (±10 minutes). If the 60-minute infusion is well-tolerated, all subsequent infusions may be administered over 30 minutes (±10 minutes).
Reference Drug, Dose and Regimen: During the Induction Study Period, 15 mg/kg IV of EU-Approved Avastin will be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles. Paclitaxel 200 mg/m^2 IV and carboplatin AUC 6 IV also will be administered on Day 1 of each cycle and will be repeated every 3 weeks up to 6 cycles (at least 4 cycles). After the Induction Study Period, EU-Approved Avastin as a monotherapy will be maintained every 3 weeks until PD or intolerable toxicity occurrence. Dose reduction of EU-Approved Avastin for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. EU-Approved Avastin will be diluted in a total volume of 100 mL of 0.9% sodium chloride and administered by IV infusion with an infusion pump. The dose should be delivered over 90 minutes (±15 minutes) at the Cycle 1 of the Induction Study Period. If the infusion is well-tolerated, the infusion of the Cycle 2 of the Induction Study Period may be administered over 60 minutes (±10 minutes). If the 60-minute infusion is well-tolerated, all subsequent infusions may be administered over 30 minutes (±10 minutes).
Objectives: <u>Primary Objective</u> • To demonstrate CT-P16 is similar to EU-Approved Avastin in terms of efficacy as determined by objective response rate (ORR) up to Cycle 6 during the Induction Study Period <u>Secondary Objectives</u> • To evaluate additional efficacy profiles including ORR during the Whole Study Period, response duration, time to progression (TTP), progression-free survival (PFS), and overall survival (OS) • To evaluate the pharmacokinetics (PK) of trough serum concentration (C_{trough}) • To evaluate safety profile including immunogenicity • To evaluate quality of life (QoL)

Main Selection Criteria: Patients for stage IV or recurrent non-squamous non-small cell lung cancer (nsNSCLC) in this study will be considered for enrollment if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

Each patient must meet all of the following criteria to be randomized in this study:

1. Patient (male or female) must be ≥ 18 years of age.
2. Patient must have confirmed predominantly non-squamous non-small cell lung cancer (nsNSCLC) by hematoxylin and eosin staining or immunohistochemistry.
3. Patient must be diagnosed as recurrent disease or stage IV according to the American Joint Committee on Cancer (AJCC) Lung Cancer Staging 8th edition. Stage IV is defined as below:
    a. Separate tumor nodule(s) in a contralateral lobe, or
    b. Tumor with pleural or pericardial nodules, or
    c. Malignant pleural or pericardial effusion related to tumor, or
    d. Single or multiple extrathoracic metastases in a single organ or in multiple organs
4. Patient must have at least 1 measurable lesion by Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1. Target lesions situated in a previously irradiated area are considered measurable if recurrence has been demonstrated in such lesions.
    a. Tumor lesions: ≥ 10 mm in long axis by computerized tomography (CT) scan, or
    b. Malignant lymph nodes: ≥ 15 mm in short axis by CT scan
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (*Oken et al., 1982*).
6. Life expectancy > 6 months based on clinical judgement.
7. Negative result in both epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement which is confirmed by biopsy or cytology specimens.
8. Patient must have adequate organ function as follows. These tests must be performed within 14 days prior to Day 1 of Cycle 1.

    Bone marrow reserve:

    a. Hemoglobin ≥ 9.0 g/dL, and
    b. Absolute neutrophil count ≥ 1,500/mm^3, and
    c. Platelet count ≥ 100,000/mm^3

    Hepatic:

    a. Alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase ≤ 3.0 × upper limit of normal (ULN) (≤ 5.0 × ULN with liver metastasis), and
    b. Total bilirubin ≤ 1.5 × ULN

    Renal:

    a. Serum creatinine ≤ 1.5 × ULN, and
    b. Creatinine clearance (CrCl) rate ≥ 45 mL/min, and
    c. Urine dipstick for proteinuria < 1+ (i.e., either 0 or trace); if urine dipstick is ≥ 1+ then < 1.0 g of protein in 24 hours urine collection must be confirmed to allow participation in the study
9. Patient and their partner of childbearing potential must agree to use acceptable birth control methods throughout the study and for 6 months after the last dose of assigned treatment (see Section 6.5.2.8).

    A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is

biologically capable of having children and is sexually active. Male and female patients and their partners who have been surgically sterilized for less than 24 weeks prior to the date of informed consent must agree to use any medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential.

10. Patient has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
11. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study and must sign the informed consent form before any study specific procedures.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Patient who has predominantly squamous cell histology non-small cell lung cancer (NSCLC). If small cell elements are present, the patient is ineligible.
2. Patient who has clinically significant third-space fluid; for example, ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to Day 1 of Cycle 1.
3. Patient who has untreated central nervous system (CNS) metastases or CNS metastasis with bleeding risk at investigator's discretion and/or leptomeningeal disease. However, treated and clinically stable (asymptomatic; off steroids) brain metastases are allowed.
4. Patient who has invasion of major blood vessels. Patient with a tumor cavitation in the opinion of the investigator is likely to bleed will be excluded as well.
5. Patient who has received previous anti-cancer systemic therapy including one or more of the following(s):
    a. Cytotoxic chemotherapy for metastatic nsNSCLC,
    b. Cytotoxic chemotherapy for non-metastatic nsNSCLC within 12 months prior to Day 1 of Cycle 1,
    c. Anti-neoplastic biological therapy, immunotherapy or targeted therapy,
    d. Bevacizumab (or a bevacizumab proposed biosimilar product).
6. Patient who has received previous surgical procedure including one or more of the following(s):
    a. Surgery for metastatic nsNSCLC,
    b. Surgery for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1,
    c. Open biopsy or open pleurodesis within 28 days prior to Day 1 of Cycle 1,
    d. Core biopsy or other minor surgical procedure (e.g. placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy) within 14 days prior to Day 1 of Cycle 1.
7. Patient who has received previous anti-cancer radiotherapy including one or more of the following(s):
    a. Radiotherapy for metastatic nsNSCLC, but radiotherapy as part of the palliative therapy and/or treatment for CNS metastases completed at least 14 days prior to Day 1 of Cycle 1 is allowed,
    b. Radiotherapy for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1,
    c. Any toxicity related with radiotherapy prior to Day 1 of Cycle 1.
8. Patient who has a medical history of disease including one or more of the following(s):
    a. Clinically significant allergic reactions such as asthma, urticaria, angio-oedema, and eczematous dermatitis, hypersensitivity to any component of carboplatin, paclitaxel, bevacizumab and Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized

antibodies.

b. Cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), metabolic (including known diabetes mellitus), autoimmune disease, or pulmonary diseases classed as significant in the opinion of the investigator.

c. A known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved.

d. ≥ New York Heart Association (NYHA) class 2 (Appendix 11.7), severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities, etc.), or myocardial infarction, within 6 months prior to Day 1 of Cycle 1.

e. Malignancy or history of malignancy other than NSCLC in the past 5 years except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix.

f. Any recent infection requiring a course of systemic anti-infectives or a serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 14 days prior to Day 1 of Cycle 1.

g. Use of oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes, or evidence of bleeding diathesis or coagulopathy. However, a patient who can discontinue regular use of aspirin (> 325 mg/day) administration at least 10 days prior to the Day 1 of Cycle 1 or a patient who continues with low dose aspirin (≤ 325 mg/day) are allowed for enrollment.

h. Hemoptysis (> 2.5 mL of red blood), thrombotic or hemorrhagic event within the past 6 months prior to Day 1 of Cycle 1.

i. Vascular disease history such as cerebrovascular accident, transient ischemic attack, or thromboembolic reactions including pulmonary embolism.

j. Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months prior to Day 1 of Cycle 1.

k. Unhealed wound following surgery, significant traumatic injury within 28 days prior to Day 1 of Cycle 1, or an anticipated need for major surgery during the study.

l. Uncontrolled hypertension (defined as either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), even after treatment.

m. Uncontrolled diabetes mellitus, even after insulin treatment.

9. Patient who has a current or recent treatment (within 30 days before Day 1 of Cycle 1 or 5 half-lives, whichever is longer) with any other investigational medicinal product or device.

10. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed and male patient who is planning to have child within 6 months of the last dose of study drug administration.

11. Patient who has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, or patient is at high risk for treatment complication in the opinion of the investigator.

Assigning Patients to Treatment Groups: Patients will be randomly assigned to one of two treatment groups. The randomization will be balanced by using permuted blocks and will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

Study Design:

This study is a double-blind, randomized, active-controlled, parallel-group, Phase 3 study to compare efficacy, PK, and overall safety of CT-P16 (15 mg/kg) and EU-Approved Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin in patients with metastatic or recurrent nsNSCLC as first-line treatment.

This study will comprise 4 study periods (including Screening Period, Induction Study Period, Maintenance Study Period, and Follow-Up Period) and be completed at approximately 3 years from the enrollment of the last patient.

- Screening Period

  Screening evaluations will be completed within 28 days prior to randomization. However, screening period can be extended to 8 weeks exclusively for treating patients who have CNS metastases before starting the study treatment and all other assessments including chest and abdomen CT scan should be completed as specified in the protocol (Table 11-1). Approximately 678 patients will be randomly assigned in a 1:1 ratio to CT-P16 or EU-Approved Avastin treatment groups.

- Induction Study Period

  During the Induction Study Period, patients will receive 15 mg/kg IV of either CT-P16 or EU-Approved Avastin every 3 weeks up to 6 cycles. Patients will receive paclitaxel 200 mg/m^2 IV and carboplatin AUC 6 IV every 3 weeks up to 6 cycles (at least 4 cycles). Study drug administration will be started on the same day as randomization. If a patient has PD during or after the completion of the Induction Study Period (assessed at the end of Cycle 6) or does not enter the Maintenance Study Period due to any reason, this patient will complete the end of treatment (EOT) visit, then will directly enter the Follow-Up Period.

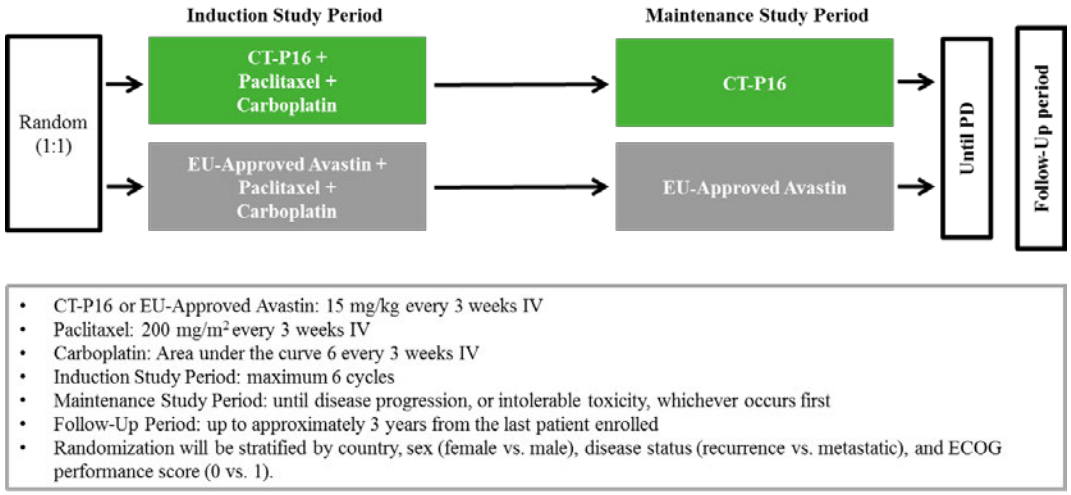
- Maintenance Study Period

  After the completion of 6 cycles during the Induction Study Period, patients with controlled disease (complete response [CR], partial response [PR] or stable disease [SD], assessed at the end of Cycle 6) will enter the Maintenance Study Period. Patients will receive monotherapy of 15 mg/kg of CT-P16 or EU-Approved Avastin every 3 weeks until PD or intolerable toxicity, whichever occurs first. Then, the patients will perform the EOT visit and then will enter the Follow-Up Period.

- Follow-Up Period

  All patients who enter the Follow-Up Period due to any reason will be followed every 9 weeks until death or the end of study, whichever occurs first. If PD is not confirmed during the Induction Study Period or Maintenance Study Period, tumor response evaluation will be performed every 9 weeks during the Follow-Up Period.

Figure S1 Study Design Overview



- CT-P16 or EU-Approved Avastin: 15 mg/kg every 3 weeks IV
- Paclitaxel: 200 mg/m^2 every 3 weeks IV
- Carboplatin: Area under the curve 6 every 3 weeks IV
- Induction Study Period: maximum 6 cycles
- Maintenance Study Period: until disease progression, or intolerable toxicity, whichever occurs first
- Follow-Up Period: up to approximately 3 years from the last patient enrolled
- Randomization will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, progressive disease.

Efficacy Assessments:

Tumor responses will be measured and recorded by using RECIST v.1.1. The primary endpoint, ORR during the Induction Study Period, and the secondary endpoint, ORR during the Whole Study Period, will be determined by the best overall response (BOR). For CR or PR, BOR must be confirmed by the subsequent assessment based on the RECIST v.1.1.

Primary Efficacy Endpoint:

- Objective response rate (ORR, %) based on BOR during the Induction Study Period by RECIST v.1.1

Secondary Efficacy Endpoints:

- ORR based on BOR during the Whole Study Period by RECIST v.1.1
- Response duration: the time between initial response (CR or PR) and PD/recurrence
- TTP: the time from randomization until PD/recurrence
- PFS: the time from randomization until PD/recurrence or death due to any cause, whichever occurs first
- OS: the time from randomization until death due to any cause

Pharmacokinetic Assessments:

- Induction Study Period (Cycle 1-6): Serum blood samples will be obtained on Day 1 of each cycle (prior to the beginning of the study drug administration).
- Maintenance Study Period: Serum blood samples will be obtained on Day 1 of Cycle 1 and every 3 cycles (end of Cycle 3, Cycle 6, Cycle 9...).
- End of treatment (EOT) visit: Serum blood samples will be obtained any time of the day.

Secondary PK Endpoints:

- C_{trough}: Trough serum concentration

Safety Assessments:

Secondary Safety Endpoints:

- Safety assessments will be performed on immunogenicity, hypersensitivity monitoring (via vital sign and ECG), vital sign measurements (blood pressure, heart rates, respiratory rates and body temperature), weight, viral assessment, physical examination, clinical laboratory analyses, ECG, ECOG, Adverse Events (AEs) (including serious adverse events [SAEs]), adverse events of special interest (AESIs) (hypersensitivity/infusion-related reactions, gastrointestinal perforations and fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome (PRES), proteinuria, arterial thromboembolism (ATE), venous thromboembolism (VTE), hemorrhages, congestive heart failure (CHF) and ovarian failure/fertility), pregnancy testing, prior and concomitant medications throughout the study. Adverse events will be reported for term and grade according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

Quality of Life Assessments:

Secondary QoL Endpoints:

- Quality of Life will be assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ). The QLQ core 30 (QLQ-C30) and QLQ lung cancer-specific module (QLQ-LC13) will be used. Patients will complete the questionnaires at Screening, end of Cycle 2, Cycle 4, and Cycle 6 of the Induction Study Period, and every 3 cycles (end of Cycle 3, Cycle 6, Cycle 9…) of the Maintenance Study Period and EOT.

Sample Size:

[redacted]

A sample size of 305 patients per group will provide 80% power to show similarity in efficacy between CT-P16 and EU-Approved Avastin using a 95% confidence interval (CI) (two one-sided alpha 0.025) of the difference in ORR for an equivalence margin of (±12.5).

Approximately 678 patients (339 in each group) will need to be enrolled for the anticipated drop-out rate of 10%.

Statistical Methods:

Statistical Analysis:

The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.

Continuous variables will be summarized by reporting the number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.

Definition of analysis Population:

Intent-to-treat (ITT) Population: The ITT population is defined as all patients randomly assigned to study drug, regardless of whether or not any study treatment dosing is completed. Patients will be assigned to treatment groups based on randomization.

Per-Protocol (PP) Population: The PP population is defined as all randomly assigned patients who have at least one response evaluation after receiving at least one full dose of study drug (CT-P16 or EU-Approved Avastin) in the Induction Study Period and who do not have any major protocol deviation. A major protocol deviation is one that may affect the interpretation of primary endpoint and it will be defined in the SAP. Final determinations of the PP population will be made at the blinded data review meeting before unblinding. Patients will be assigned to treatment groups based on randomization.

PK Population: The PK population is defined as all patients who receive at least one full dose of study drug (CT-P16 or EU-Approved Avastin) and who have at least one post treatment PK result. If any patients are found to be non-compliant with respect to dosing, a decision will be made on a case-by-case basis at the blinded data review meeting before unblinding. Patients will be assigned to treatment groups based on treatment actually received.

Safety Population: The safety population is defined as all randomly assigned patients who receive at least one dose (full or partial) of study drug (CT-P16 or EU-Approved Avastin). Patients will be assigned to treatment groups based on treatment actually received.

Data analyses:

The study will be unblinded to the pre-defined unblinded personnel from the Sponsor and contract research organization (CRO) after the completion of Cycle 6 of the Induction Study Period in all patients for the reporting purposes. The unblinded personnel will be pre-defined before breaking the study blind. The study will remain blinded to the investigators, patients and pre-defined blinded personnel from the Sponsor and CRO until all patients have completed the study and the database has been finalized for study completion.

Efficacy Analysis:

The similarity criterion has been set such that the confidence limits of the 95% CI of the difference in ORR will be entirely bounded by the interval (-12.5, 12.5). The primary analysis for the primary endpoint will be performed utilizing a logistic regression model considering covariates with treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect in the ITT and PP population. For primary analysis, central review result will be used. Local review result will be used as supportive data (sensitivity analysis). The resulting odds ratio and 95% CI will be converted into difference of proportions using the Delta method for the purpose of comparison. Covariates will be described in the SAP.

The secondary endpoint, both locally reviewed ORR and centrally reviewed ORR during the Whole Study Period, will be summarized using proportion and its corresponding 95% CI for each treatment group in the ITT and PP population.

A time-to-event analysis will be undertaken for each of the response duration, TTP, PFS, and OS in the ITT and PP population; the median time and its corresponding 95% CI for each treatment group for each secondary endpoint of time-to-event analysis will be estimated using the Kaplan-Meier method.

Pharmacokinetic Analysis:

The C_{trough} (prior to next dose) at each cycle during the Induction Study Period, and C_{trough} during the Maintenance Study Period will be analyzed. Serum concentrations will be summarized using descriptive statistics (including geometric mean and coefficient of variation [CV], as appropriate) by treatment, and study visit. Pharmacokinetic parameters will also be summarized using descriptive statistics (including geometric mean and CV, as appropriate) by treatment and study visit. All analyses will be performed based on the PK population.

Safety Analysis:

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded for severity according to the CTCAE v.5.0. Prior and concomitant medication will be coded to drug class and PT using the World Health Organization (WHO) drug dictionary.

All safety data including immunogenicity will be listed and summarized by treatment group in the safety population.

Quality of Life Analysis:

Descriptive analysis will be performed on actual score and change from baseline at each visit by treatment group in the ITT population.

List of Abbreviations

Abbreviation	Definition
Study drug	CT-P16 or EU-Approved Avastin
Study treatment	CT-P16 or EU-Approved Avastin in combination with paclitaxel and carboplatin
ADL	activity of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ATE	arterial thromboembolism
AUC	area under the curve
BOR	best overall response
CFR	Code of Federal Regulation
CHF	congestive heart failure
CHO	Chinese Hamster Ovary
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CRO	Contract Research Organization
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration
CV	coefficient of variation
DNA	deoxyribonucleic acid
DRR	death rate ratio
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor

Abbreviation	Definition
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
mCRC	metastatic carcinoma of the colon or rectum
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
nsNSCLC	non-squamous non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PP	per protocol
PR	partial response

Abbreviation	Definition
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
PVG	pharmacovigilance
QLQ-C30	Quality of Life Questionnaire core 30
QLQ-LC13	Quality of Life Questionnaire lung cancer specific module
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TTP	time to progression
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
VEGF	Vascular Endothelial Growth Factor
VTE	venous thromboembolism
WHO	World Health Organization

1 Introduction

1.1 Background

In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States (US). Over the past decade of data, the cancer incidence rate (2005-2014) was stable in women and declined by approximately 2% annually in men, while the cancer death rate (2006-2015) declined by about 1.5% annually in both men and women. The combined cancer death rate dropped continuously from 1991 to 2015 by a total of 26%, translating to approximately 2,378,600 fewer cancer deaths than would have been expected if death rates had remained at their peak. Of the 10 leading causes of death, only cancer declined from 2014 to 2015. In 2015, the cancer death rate was 14% higher in non-Hispanic blacks than non-Hispanic whites overall (death rate ratio [DRR], 1.14; 95% confidence interval [95% CI], 1.13-1.15), but the racial disparity was much larger for individuals aged <65 years (DRR, 1.31; 95% CI, 1.29-1.32) compared with those aged ≥ 65 years (DRR, 1.07; 95% CI, 1.06-1.09) and varied substantially by state (*Siegel et al., 2018*).

An estimated 234,030 new cases of lung cancer will be diagnosed in the US in 2018. The incidence rate has been declining since the mid-1980s in men, but only since the mid-2000s in women, because of gender differences in historical patterns of smoking uptake and cessation. From 2005 to 2014, lung cancer incidence rates decreased by 2.5% per year in men and 1.2% per year in women. An estimated 154,050 deaths from lung cancer will occur in 2018. The lung cancer death rate has declined by 45% since 1990 in men and by 19% since 2002 in women due to reductions in smoking, with the pace of decline quickening over the past decade; from 2011 to 2015, the rate decreased by 3.8% per year in men and by 2.3% per year in women. The 5-year relative survival rate for lung cancer is 18% (15% for men and 21% for women). Only 16% of lung cancers are diagnosed at a localized stage, for which the 5-year survival rate is 56% (*American Cancer Society 2018, GLOBOCAN 2012*).

The early signs and symptoms of lung cancer are non-specific and as a consequence the majority of cases are diagnosed at an advanced stage, making successful treatment more difficult and survival outcomes poor (*Barzi and Pennell 2010*). There are two main types of lung cancer; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Non-small cell lung cancer is the most commonly diagnosed type of lung cancer, accounting for approximately 85% of all cases (*Barzi and Pennell 2010*). Non-small cell lung cancer comprises a number of different types of lung cancer, which are grouped as 'squamous' or 'non-squamous'. Non-squamous non-small cell lung cancer (nsNSCLC) includes further subtypes such as adenocarcinoma and large cell carcinoma (*NCCN - Non-Small Cell Lung Cancer 2018*). Approximately 80% of NSCLC cases are non-squamous and 20% are squamous histology. In this study, CT-P16 is being evaluated in patients with nsNSCLC.

Cigarette smoking is by far the most important risk factor for lung cancer; 80% of lung cancer deaths in the US are still caused by smoking. Risk increases with both quantity and duration of smoking. Cigar and pipe smoking also increase risk. Exposure to radon gas released from soil and building materials is thought to be the second-leading cause of lung cancer in the US. Other risk factors include occupational or environmental exposure to secondhand smoke, asbestos (particularly among smokers), certain metals (chromium, cadmium, and arsenic), some organic chemicals, radiation, air pollution, and diesel exhaust. Some specific occupational exposures that increase risk include rubber manufacturing, paving, roofing, painting, and chimney sweeping. Risk is also probably increased among people with a history of tuberculosis. Genetic susceptibility (e.g., family history) plays a role in the development of lung cancer, especially in those who develop the disease at a young age (*American Cancer Society 2018*).

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (*SmPC Avastin 2018*).

1.2 CT-P16

CT-P16 is a recombinant humanized monoclonal antibody that is being developed and manufactured as a biosimilar to Avastin (bevacizumab) by CELLTRION, Inc. CT-P16 will have the same pharmaceutical form and strength as Avastin, and is intended to be analytically highly similar to Avastin. Bevacizumab, the active ingredient of CT-P16, is

produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary (CHO) cell expression system and purified by a suitable process.

CT-P16, containing the active ingredient of bevacizumab, is a humanized monoclonal antibody that targets VEGF, neutralizes human VEGF and inhibits VEGF-induced proliferation of endothelial cells that is being developed as a similar biological medicinal product to Avastin. Avastin (bevacizumab) was initially authorized in the European Union (EU) on 12 January 2005 for the treatment of metastatic carcinoma of the colon or rectum (mCRC) in combination with fluoropyrimidine-based chemotherapy. In the EU, it is currently approved in combination with other medicines to treat mCRC, metastatic breast cancer, NSCLC, advanced and/or metastatic renal cell cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer, recurrent glioblastoma, persistent or recurrent cervical cancer, and metastatic carcinoma of the cervix (*SmPC Avastin 2018*). In the US, Avastin (bevacizumab) was authorized on 26 February 2004 for the treatment of mCRC in combination with 5-fluorouracil–based chemotherapy and is currently approved in combination with other medicines to treat mCRC, nsNSCLC, recurrent glioblastoma, metastatic renal cell cancer, persistent, recurrent, or metastatic cervical cancer, and recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (*Avastin USPI 2018*).

Avastin is supplied as a sterile, preservative-free solution of bevacizumab for intravenous (IV) administration. Avastin is supplied in 1 strength, 25 mg/mL, as 100 mg/4 mL vial and 400 mg/16 mL vial.

CT-P16 is manufactured using a CHO cell line by fed-batch cell culture, followed by harvest, purification, formulation, and subsequent fill-finish operations. The amino acid sequences in CT-P16 are identical to that of Avastin. Like Avastin, CT-P16 will be supplied as a sterile, clear to opalescent, colorless to brown, preservative-free liquid at a concentration of 25 mg/mL in 400 mg (16 mL) vials for IV infusion. CT-P16 will have the same pharmaceutical form and strength as Avastin.

1.3 Non-clinical Studies

Detailed information regarding the non-clinical pharmacology and toxicology of CT-P16 can be found in the investigator's brochure (IB).

1.4 Clinical Studies

CT-P16 has been administered to humans. The pharmacokinetic (PK) of Avastin (bevacizumab) in healthy male subjects was assessed in multicenter, randomized, double-blind, three-arm phase 1 study (NCT03247673). In this study a single dose of 5 mg/kg of either CT-P16, EU-Approved Avastin, or US-Licensed Avastin was administered to healthy male subjects to demonstrate the similarity of PK. The PK results were contained within the pre-defined bioequivalence margin, indicating bioequivalence between CT-P16, EU-Approved Avastin, and US-Licensed Avastin. The overall safety profiles were similar between CT-P16, EU-Approved Avastin, and US-Licensed Avastin. As CT-P16 is being developed as a similar biological medicinal product, reference is made to the published clinical information on Avastin (bevacizumab). The reference information is summarized in the clinical section of the IB.

In nsNSCLC, the proven efficacy and well-established safety profile of bevacizumab as a first-line treatment have been demonstrated in 2 randomized Phase 3 trials.

The Eastern Cooperative Oncology Group (ECOG) Phase 3 trial E4599 reported significantly improved overall survival (OS; study primary endpoint) with bevacizumab plus carboplatin–paclitaxel versus carboplatin–paclitaxel alone (hazard ratio 0.79; median 12.3 versus 10.3 months; P = 0.003). Bevacizumab plus carboplatin–paclitaxel also significantly improved progression-free survival (PFS) and response rates versus carboplatin–paclitaxel alone and had an acceptable safety profile. The results of E4599 showed that bevacizumab is the first agent to increase OS beyond the historical 1-year benchmark (*Sandler et al., 2006*).

AVAiL (BO17704) study, a randomized placebo-controlled Phase 3 trial, evaluated bevacizumab (7.5 and 15 mg/kg every 3 weeks) in combination with cisplatin/gemcitabine. In AVAiL study, the primary endpoint of PFS was met, further proving the efficacy of bevacizumab in NSCLC (*Reck et al., 2009*).

The positive results from AVAiL study, together with those from the E4599 study, demonstrate that bevacizumab combined with standard platinum-based chemotherapy doublets in the first-line setting leads to significantly improved outcomes for patients with advanced nsNSCLC.

1.5 Study Rationale

CT-P16 is currently being developed by CELLTRION, Inc., which is intended to be formulated as biosimilar to Avastin. For a biosimilar to be approved, it must be shown that there are no clinical differences between the two products. The stepwise 'totality of evidence' approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis. However, statistically proven equivalence between biosimilar and Avastin in both PK and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. The PK profile of CT-P16, EU-Approved Avastin, and US-Licensed Avastin demonstrated PK equivalence in a Phase 1 study in healthy male subjects. An additional assessment of the similarity in efficacy, PK, safety, and immunogenicity will be carried out in this proposed comparative clinical trial (Study CT-P16 3.1) in patients with metastatic or recurrent nsNSCLC. CELLTRION, Inc. considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence of CT-P16 (Study CT-P16 1.1; Phase 1; PK similarity healthy volunteer study) and therapeutic equivalence and safety (Study CT-P16 3.1; Phase 3; comparative clinical similarity) to Avastin.

1.5.1 Choice of Study Population

International regulations (*WHO 2009, European Medicines Agency 2012, FDA 2015*) suggest that proposed biosimilars should be tested in a population representative of approved therapeutic indications of Avastin and sufficiently sensitive for detecting potential differences between the biosimilar and Avastin.

The eligibility criteria for the Study CT-P16 3.1 have been designed to select a homogenous patient population appropriate for treatment with Avastin, per the US/EU-Approved indication. Avastin is indicated, in addition to platinum-based chemotherapy, for first-line treatment of patients with unresectable advanced, metastatic or recurrent nsNSCLC (*Avastin USPI 2018, SmPC Avastin 2018*). Accordingly, eligible patients must be diagnosed with stage IV or recurrent nsNSCLC, and planning to initiate first-line platinum-based chemotherapy after randomization. These criteria are similar to those in the pivotal placebo-controlled study in this indication for the innovator product (*Sandler et al., 2006*), in which a statistically and clinically significant effect was demonstrated for bevacizumab versus placebo. Per applicable guidelines, a sponsor should consider whether a study in a specific population will be sufficiently sensitive to detect

clinically meaningful differences (*He et al., 2016*). The effect of bevacizumab on objective response rate (ORR) in NSCLC patients documented in historical studies was sufficiently large and clinically meaningful because of correlations with improvement in PFS and OS (*Botrel et al., 2011*). Recently approved by Food and Drug Administration (FDA), bevacizumab biosimilar ABP215 (*SmPC MVASI 2019*) was evaluated in the pivotal comparative efficacy study in patients with nsNSCLC using ORR as a primary endpoint. Given these considerations, CELLTRION, Inc. believes that this is a homogenous and sensitive population to demonstrate the effect of bevacizumab and to compare the relative efficacy and safety of Avastin and CT-P16.

1.6 Benefit and Risk Assessment

The CT-P16 will have the same pharmaceutical form and strength as Avastin (25 mg/mL). The proposed dosing regimen is in line with the approved labeling for Avastin (*SmPC Avastin 2018*, *Avastin USPI 2018*).

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P16 administration. In view of the structural, biological, and toxicological similarity to Avastin, CT-P16 is expected to display a similar safety profile.

Based upon the clinical evidence (Section 1.4) as well as the proven safety profile of Avastin, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

2 Study Objectives

2.1 Primary Objective

- To demonstrate CT-P16 is similar to EU-Approved Avastin in terms of efficacy as determined by ORR up to Cycle 6 during the Induction Study Period

2.2 Secondary Objectives

- To evaluate additional efficacy profiles including ORR during the Whole Study Period, response duration, time to progression (TTP), PFS, and OS
- To evaluate the PK of trough serum concentration (C_{trough})
- To evaluate safety profile including immunogenicity
- To evaluate quality of life (QoL)

3 Investigational Plan

3.1 Study Design

This study is a double-blind, randomized, active-controlled, parallel-group, Phase 3 study to compare efficacy, PK, and overall safety of CT-P16 (15 mg/kg) and EU-Approved Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin in patients with metastatic or recurrent nsNSCLC as first-line treatment.

A total of 678 male and female patients with metastatic or recurrent nsNSCLC will be enrolled and randomly assigned in a 1:1 ratio (approximately 339 patients per treatment group) to CT-P16 or EU-Approved Avastin.

This study will comprise 4 study periods (including Screening Period, Induction Study Period, Maintenance Study Period and Follow-Up Period) and be completed at approximately 3 years from the enrollment of last patient.

An end of treatment (EOT) visit will occur 3 weeks after the last dose of the Induction Study Period or Maintenance Study Period regardless of the reason of discontinuation.

Screening Period

Screening evaluations will be completed within 28 days prior to randomization. However, screening period can be extended to 8 weeks exclusively for treating patients who have CNS metastases before starting the study treatment and all other assessments including chest and abdomen CT scan should be completed as specified in the protocol (Table 11-1). Approximately 678 patients will be randomly assigned in a 1:1 ratio to CT-P16 or EU-Approved Avastin treatment groups.

Induction Study Period

During the Induction Study Period, patients will receive 15 mg/kg IV of either CT-P16 or EU-Approved Avastin every 3 weeks up to 6 cycles. Patients will receive paclitaxel 200 mg/m^2 IV and carboplatin area under the curve (AUC) 6 IV every 3 weeks up to 6 cycles (at least 4 cycles). Study drug administration will be started on the same day as randomization. If a patient has progressive disease (PD) during or after the completion of the Induction Study Period (assessed at the end of Cycle 6) or does not enter the

Maintenance Study Period due to any reason, this patient will complete the EOT visit, then will directly enter the Follow-Up Period.

Maintenance Study Period

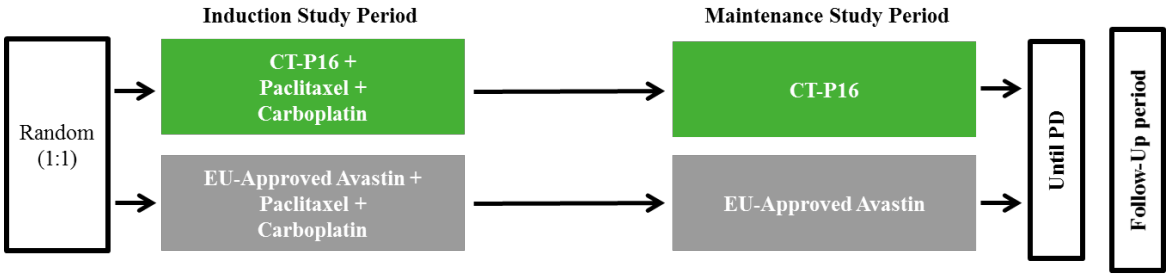
After the completion of 6 cycles during the Induction Study Period, patients with controlled disease (complete response [CR], partial response [PR], or stable disease [SD], assessed at the end of Cycle 6) will enter the Maintenance Study Period. Patients will receive monotherapy of 15 mg/kg of CT-P16 or EU-Approved Avastin every 3 weeks until PD or intolerable toxicity, whichever occurs first. Then, the patients will perform the EOT visit and then will enter the Follow-Up Period.

Follow-Up Period

All patients who enter the Follow-Up Period due to any reason will be followed every 9 weeks until death or the end of study, whichever occurs first. If PD is not confirmed during the Induction Study Period or Maintenance Study Period, tumor response evaluation will be performed every 9 weeks during the Follow-Up Period.

The study design and patient assessment overview is presented in Figure 1.

Figure 1 Study Design Overview



- CT-P16 or EU-Approved Avastin: 15 mg/kg every 3 weeks IV
- Paclitaxel: 200 mg/m^2 every 3 weeks IV
- Carboplatin: Area under the curve 6 every 3 weeks IV
- Induction Study Period: maximum 6 cycles
- Maintenance Study Period: until disease progression, or intolerable toxicity, whichever occurs first
- Follow-Up Period: up to approximately 3 years from the last patient enrolled
- Randomization will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, progressive disease.

3.1.1 Rationale of Study Design

The primary objective of the study is to demonstrate the efficacy equivalence in terms of ORR between CT-P16 and EU-Approved Avastin. Taking into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibody: Non-clinical and Clinical Issues (*European Medicines Agency 2012*) and the FDA Guideline for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (*FDA 2007*), ORR is selected as a primary endpoint for this study. Objective response rate is considered a clinically relevant, objective and sensitive endpoint for the purpose of the clinical similarity assessment of the proposed bevacizumab biosimilar.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 678 patients will be enrolled at approximately 150 study centers in around 23 countries. Male or female patients with metastatic or recurrent nsNSCLC will be considered for enrollment in the study if they meet all the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be randomized in this study:

1. Patient (male or female) must be ≥ 18 years of age.
2. Patient must have confirmed predominantly non-squamous non-small cell lung cancer (nsNSCLC) by hematoxylin and eosin staining or immunohistochemistry.
3. Patient must be diagnosed as recurrent disease or stage IV according to the American Joint Committee on Cancer (AJCC) Lung Cancer Staging 8th edition. Stage IV is defined as below:
    a. Separate tumor nodule(s) in a contralateral lobe, or
    b. Tumor with pleural or pericardial nodules, or
    c. Malignant pleural or pericardial effusion related to tumor, or
    d. Single or multiple extrathoracic metastases in a single organ or in multiple organs
4. Patient must have at least 1 measurable lesion by Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1. Target lesions situated in a previously irradiated area are considered measurable if recurrence has been demonstrated in such lesions.
    a. Tumor lesions: ≥ 10 mm in long axis by computerized tomography (CT) scan, or
    b. Malignant lymph nodes: ≥ 15 mm in short axis by CT scan
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (*Oken et al., 1982*).
6. Life expectancy > 6 months based on clinical judgement.

7. Negative result in both epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement which is confirmed by biopsy or cytology specimens.

8. Patient must have adequate organ function as follows. These tests must be performed within 14 days prior to Day 1 of Cycle 1.

   Bone marrow reserve:

   a. Hemoglobin ≥ 9.0 g/dL, and
   b. Absolute neutrophil count ≥ 1,500/mm^3, and
   c. Platelet count ≥ 100,000/mm^3

   Hepatic:

   a. Alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase ≤ 3.0 × upper limit of normal (ULN) (≤ 5.0 × ULN with liver metastasis), and
   b. Total bilirubin ≤ 1.5 × ULN

   Renal:

   a. Serum creatinine ≤ 1.5 × ULN, and
   b. Creatinine clearance (CrCl) rate ≥ 45 mL/min, and
   c. Urine dipstick for proteinuria < 1+ (i.e., either 0 or trace); if urine dipstick is ≥ 1+ then < 1.0 g of protein in 24 hours urine collection must be confirmed to allow participation in the study

9. Patient and their partner of childbearing potential must agree to use acceptable birth control methods throughout the study and for 6 months after the last dose of assigned treatment (see Section 6.5.2.8).

   A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active. Male and female patients and their partners who have been surgically sterilized for less than 24 weeks prior to the date of informed consent must agree to use any medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential.

10. Patient has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
11. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study and must sign the informed consent form before any study specific procedures.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patient who has predominantly squamous cell histology non-small cell lung cancer (NSCLC). If small cell elements are present, the patient is ineligible.
2. Patient who has clinically significant third-space fluid; for example, ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to Day 1 of Cycle 1.
3. Patient who has untreated central nervous system (CNS) metastases or CNS metastasis with bleeding risk at investigator's discretion and/or leptomeningeal disease. However, treated and clinically stable (asymptomatic; off steroids) brain metastases are allowed.
4. Patient who has invasion of major blood vessels. Patient with a tumor cavitation in the opinion of the investigator is likely to bleed will be excluded as well.
5. Patient who has received previous anti-cancer systemic therapy including one or more of the following(s):
    a. Cytotoxic chemotherapy for metastatic nsNSCLC,
    b. Cytotoxic chemotherapy for non-metastatic nsNSCLC within 12 months prior to Day 1 of Cycle 1,
    c. Anti-neoplastic biological therapy, immunotherapy or targeted therapy,
    d. Bevacizumab (or a bevacizumab proposed biosimilar product).
6. Patient who has received previous surgical procedure including one or more of the following(s):
    a. Surgery for metastatic nsNSCLC,
    b. Surgery for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1,

c. Open biopsy or open pleurodesis within 28 days prior to Day 1 of Cycle 1,

d. Core biopsy or other minor surgical procedure (e.g. placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy) within 14 days prior to Day 1 of Cycle 1.

7. Patient who has received previous anti-cancer radiotherapy including one or more of the following(s):

   a. Radiotherapy for metastatic nsNSCLC, but radiotherapy as part of the palliative therapy and/or treatment for CNS metastases completed at least 14 days prior to Day 1 of Cycle 1 is allowed,

   b. Radiotherapy for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1,

   c. Any toxicity related with radiotherapy prior to Day 1 of Cycle 1.

8. Patient who has a medical history of disease including one or more of the following(s):

   a. Clinically significant allergic reactions such as asthma, urticaria, angio-oedema, and eczematous dermatitis, hypersensitivity to any component of carboplatin, paclitaxel, bevacizumab and Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies.

   b. Cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), metabolic (including known diabetes mellitus), autoimmune disease, or pulmonary diseases classed as significant in the opinion of the investigator.

   c. A known infection with hepatitis B (active or carrier of hepatitis B), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved.

   d. ≥ New York Heart Association (NYHA) class 2 (Appendix 11.7), severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities, etc.), or myocardial infarction, within 6 months prior to Day 1 of Cycle 1.

   e. Malignancy or history of malignancy other than NSCLC in the past 5 years except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix.

f. Any recent infection requiring a course of systemic anti-infectives or a serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 14 days prior to Day 1 of Cycle 1.

g. Use of oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes, or evidence of bleeding diathesis or coagulopathy. However, a patient who can discontinue regular use of aspirin (> 325 mg/day) administration at least 10 days prior to the Day 1 of Cycle 1 or a patient who continues with low dose aspirin (≤ 325 mg/day) are allowed for enrollment.

h. Hemoptysis (> 2.5 mL of red blood), thrombotic or hemorrhagic event within the past 6 months prior to Day 1 of Cycle 1.

i. Vascular disease history such as cerebrovascular accident, transient ischemic attack, or thromboembolic reactions including pulmonary embolism.

j. Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months prior to Day 1 of Cycle 1.

k. Unhealed wound following surgery, significant traumatic injury within 28 days prior to Day 1 of Cycle 1, or an anticipated need for major surgery during the study.

l. Uncontrolled hypertension (defined as either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), even after treatment.

m. Uncontrolled diabetes mellitus, even after insulin treatment.

9. Patient who has a current or recent treatment (within 30 days before Day 1 of Cycle 1 or 5 half-lives, whichever is longer) with any other investigational medicinal product or device.

10. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed and male patient who is planning to have child within 6 months of the last dose of study drug administration.

11. Patient who has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, or patient is at high risk for treatment complication in the opinion of the investigator.

4.2 Withdrawal of Patients from the Study

Patients are free to withdraw from the study at any time for any reason. The investigator may also withdraw the patient at any time in the interest of patient safety. The primary reason for withdrawal must be recorded in the patient's medical record and on the withdrawal form in the electronic case report form (eCRF) and source documents.

When possible, the sponsor should be notified of the withdrawal of a patient from the study. For patients who withdraw before the end of the study treatment, an EOT visit will occur 3 weeks after the last dose of the Induction Study Period or Maintenance Study Period regardless of the reason for discontinuation. Any comments (spontaneous or elicited) or complaints made by the patient, together with the reason for the study treatment termination, and the date of cessation of study drug must be recorded in the eCRF and source documents. It is vital to obtain follow-up data on any patient withdrawn because of an adverse event (AE) or serious adverse event (SAE). In every case, efforts must be made to undertake protocol-specified safety and follow-up procedures.

Reasons for withdrawal from the study treatment include the following:

- Patient develops signs of disease progression in the judgement of the investigator.
- Patient withdraws consent or refuses to continue treatment and/or procedures/observations.
- Patient has any AE that would compromise his or her safety if he or she continues to participate in the study.
- Patient has a significant protocol deviation(s).
- Patient is lost to follow-up.
- Patient dies.
- Study is terminated by the Sponsor.
- Patient is pregnant.

- Investigator's decision.

The sponsor may contact or be contacted if clarification is required on a case-by-case basis.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and discontinue before study completion will not be replaced. Patients who are screen failed, for any reason, can be re-screened only once. Re-screened patient will be assigned with new patient identification.

4.3 Premature Discontinuation of the Study

The sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As much as possible, this should occur after mutual consultation.

If the study is terminated prematurely by the sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the institutional review board (IRB) or independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

An interactive voice response system (IVRS) or an interactive web response system (IWRS) will be used for the randomization. A randomization schedule will be generated for IVRS or IWRS, which will link sequential patient randomization numbers to treatment codes.

Patients who qualify for randomization will be randomly assigned on Day 1 of Cycle 1 of the Induction Study Period in a 1:1 ratio to receive CT-P16 or EU-Approved Avastin. The randomization will be balanced by using permuted blocks and will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1) (Appendix 11.4).

5.2 Identity of Investigational Product

CT-P16 is a recombinant humanized monoclonal antibody which is being developed by CELLTRION, Inc. as a potential biosimilar to Avastin.

Dosing instruction described in Avastin prescribing information is to be followed (*Avastin USPI 2018, SmPC Avastin 2018*).

The company code of the product is CT-P16. The International Nonproprietary Name of the commercially available reference material (Avastin) is bevacizumab. Bevacizumab contains in total 1,334 amino acids and has an approximate molecular weight of 149 kDa. It is composed of 2 identical light chains (214 amino acids each) and 2 heavy chains (453 amino acids each). The 2 heavy chains are covalently coupled to one another through 2 inter-chain disulphide bonds, and each light chain is covalently coupled to a heavy chain through a disulphide bond (cysteine 214 to cysteine 226, respectively).

CT-P16 will be supplied as a sterile, clear to opalescent, colorless to brown, preservative-free liquid at a concentration of 25 mg/mL in 400 mg (16 mL) vials for IV infusion.

EU-Approved Avastin will be supplied as a clear, colorless to pale brown liquid in a glass vial with a rubber stopper. Each vial contains 400 mg bevacizumab in 16 mL (25mg/ml) of solution (*SmPC Avastin 2018*).

CELLTRION, Inc. will provide adequate supplies of CT-P16 and EU-Approved Avastin for distribution to the study centers.

The following drug supplies will be used in the study:

Product	Supplied as:
CT-P16	25 mg/mL in 400 mg (16 mL) vials
EU-Approved Avastin	25 mg/mL in 400 mg (16 mL) vials

The drug supplies will have the following excipients.

Component	CT-P16 Drug Product	EU-Approved Avastin
API	25 mg/mL	25 mg/mL
Sodium phosphate	51 mM	51 mM
α, α -trehalose dihydrate	60 mg/mL	60 mg/mL
Polysorbate 20	0.04 %	0.04 %

Abbreviation: API, active pharmaceutical ingredient

5.3 Treatments Administered

During the Induction Study Period, study treatment will be administered in following order:

Hydration (by local practice)

Dexamethasone 20 mg
Oral, approximately 12 and 6 hours prior to administration of paclitaxel *or*
IV infusion, 30 to 60 minutes prior to administration of paclitaxel

Diphenhydramine (or its equivalent) 50 mg
IV infusion 30 to 60 minutes prior to administration of paclitaxel

Cimetidine 300 mg or ranitidine 50 mg
IV infusion 30 to 60 minutes prior to administration of paclitaxel

⬇

Paclitaxel 200 mg/m^2
IV infusion over approximately 3 hours

⬇

Carboplatin AUC 6.0
IV infusion over approximately 30 minutes after administration of paclitaxel

⬇

CT-P16 or EU-Approved Avastin 15 mg/kg
IV infusion over 30 to 90 minutes after administration of carboplatin

Note: Antiemetic can be used based on local practice. Dose of dexamethasone, diphenhydramine, and cimetidine can be adjusted at the investigator's discretion.

Uncoupling of study treatment is not allowed until at least 4 cycles of the Induction Study Period have been completed.

- Study treatment (CT-P16 or EU-Approved Avastin, carboplatin, and paclitaxel) should be administered on the same date.
- If one of them should be delayed, study treatment should be delayed.

- If one of them should be permanently discontinued, study treatment should be discontinued.

However, paclitaxel and/or carboplatin can be discontinued at Cycle 5 or 6 of Induction Study Period based on Section 5.4.1.2.

Body weight on Day 1 of each cycle during the Induction Study Period and Maintenance Study Period will be used for each administration.

Further information of dosing time and details for Induction Study Period and Maintenance Study Period are specified in each section.

Treatment during the Induction Study Period and Maintenance Study Period can be delayed for up to 3 weeks from the planned schedule. If treatment is delayed more than 3 weeks, then the patient will be discontinued.

5.3.1 CT-P16 and EU-Approved Avastin

During the Induction Study Period, patients will receive 15 mg/kg IV of either CT-P16 or EU-Approved Avastin every 3 weeks up to 6 cycles. Patients will receive paclitaxel 200 mg/m^2 IV and carboplatin AUC 6 IV every 3 weeks up to 6 cycles (at least 4 cycles). After the Induction Study Period, either CT-P16 or EU-Approved Avastin as a monotherapy (15 mg/kg IV) will be maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurs first.

CT-P16 or EU-Approved Avastin will be diluted in a total volume of 100 mL of 0.9% sodium chloride and administered by IV infusion with an infusion pump. The dose should be delivered over 90 minutes (±15 minutes) at the Cycle 1 of the Induction Study Period. If the infusion is well-tolerated, the infusion of the Cycle 2 of the Induction Study Period may be administered over 60 minutes (±10 minutes). If the 60-minute infusion is well-tolerated, all subsequent infusions may be administered over 30 minutes (±10 minutes).

The study drug is required to be handled by delegated unblinded staff.

No premedication is required prior to administration of study drug.

5.3.2 Paclitaxel

Paclitaxel will be administered at a dose of 200 mg/m^2 approximately 3 hours through an in-line filter with a microporous membrane not greater than 0.22 microns using a single infusion, per local practice guidelines.

Paclitaxel will be diluted in 0.9% sodium chloride or 5% dextrose. Paclitaxel will be administered on Day 1 of each cycle in Induction Study Period and will be repeated every 3 weeks from Cycle 1 through Cycle 6. Paclitaxel can be discontinued at Cycle 5 or 6 of Induction Study Period based on Section 5.4.1.2.

Description for Calculation method

For dose amount calculation, the body surface area (BSA) should be calculated using either Mosteller formula or Dubois formula (*Dubois and Dubois 1916*, *Mostella 1987*).

- Mosteller formula: BSA (m^2) = sqrt ([height (cm) x weight (kg)]/3600)
- Dubois formula: BSA (m^2) = 0.007184 x [Weight (kg)]$^{0.425}$ x [height (cm)]$^{0.725}$

All patients should be pre-treated with corticosteroids, antihistamines, and H_2 antagonists:

- Dexamethasone 20 mg: via per oral approximately 12 and 6 hours before paclitaxel, or via IV 30 to 60 minutes prior to paclitaxel
- Diphenhydramine (or its equivalent) 50 mg: via IV 30 to 60 minutes prior to paclitaxel
- Cimetidine 300 mg or ranitidine 50 mg: via IV 30 to 60 minutes before paclitaxel.

Paclitaxel should be administered only when the hematology and non-hematology toxicity criteria described in Section 5.4.1.2.1 are met.

5.3.3 Carboplatin

Carboplatin will be administered at a dose of AUC 6 approximately 30 minutes using a single infusion, per local practice guidelines.

Carboplatin will be diluted in 0.9% sodium chloride or 5% dextrose. Carboplatin will be administered after the dose of paclitaxel and before the dose of study drug (Day 1 of each cycle in Induction Study Period). Carboplatin will be repeated every 3 weeks from Cycle 1 through Cycle 6. Carboplatin can be discontinued at Cycle 5 or 6 of Induction Study Period based on Section 5.4.1.2.

Description for Calculation method

The dose of carboplatin will be calculated based on Calvert equation (*Calvert et al., 1989*).

- Maximum carboplatin dose (mg) = target AUC 6 (mg·min/mL) x (125 mL/min + 25) = 6 mg·min/mL x 150 mL/min = 900 mg

- Carboplatin dose (mg) = target AUC 6 (mg·min/mL) x (GFR* + 25)

*Glomerular filtration rate (GFR) estimated by calculated CrCl using Cockcroft-Gault Equation

Further details about calculated CrCl formula for men and women are provided in Appendix 11.6.

No premedication is required prior to administration of carboplatin.

Carboplatin should be administered only when the hematology and non-hematology toxicity criteria described in Section 5.4.1.2.1 are met.

5.4 Guidelines for Dosing

5.4.1 Dose Modification and Discontinuation

Dose reduction will not be allowed for study drug (CT-P16 and EU-Approved Avastin). Details regarding temporary discontinuation of study drug are provided in Section 5.4.1.1.

For carboplatin and paclitaxel, dose reduction will be allowed maximum of 2 times (2 cycles). Dose reduction will be counted by cycle. Dose reduction in 1 cycle will be counted as once. Examples include the following:

	Paclitaxel	Carboplatin	Reduction
Cycle 2	Reduction	No reduction	First reduction
Cycle 3	Another reduction	Reduction	Second reduction
Cycle 4	Another reduction	Another Reduction	Third reduction – not allowed

5.4.1.1 CT-P16 or EU-Approved Avastin

Study drug (CT-P16 or EU-Approved Avastin) should be withheld until recovery or permanently discontinued when a patient experience any of the events as per Table 5-1.

Table 5-1 Bevacizumab Dose Management due to Adverse Events

Event	Action to be Taken with Study Drug
Hypertension	
Grade 2 or 3	Withhold until recovery to < 140/90 mmHg with/without medication
Grade 4	Permanent discontinuation
Hypertensive encephalopathy	Permanent discontinuation
Proteinuria	
Grade 2 (2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hours) or Grade 3 (urinary protein ≥ 3.5 g/24 hours; 4+ proteinuria)	Withhold until recovery to ≤ Grade 1
Wound healing complications	Withhold until the wound is fully healed
Requiring medical intervention or necrotizing fasciitis	Permanent discontinuation
Arterial thromboembolism (ATE)	Permanent discontinuation
Congestive heart failure (CHF)[1]	
Gastrointestinal perforation	

Event	Action to be Taken with Study Drug
Hemorrhage *Grade 3 or 4*	Permanent discontinuation
Intracranial hemorrhage	
Bronchopulmonary hemorrhage *Grade 2 or higher* *Hemoptysis (> 2.5 mL of red blood)*	
Hypersensitivity reactions, infusion reactions (see Section 6.5.2.2) *Grade 3 or 4*	
Nephrotic syndrome	
Non-gastrointestinal fistulae *Grade 4*	
Tracheoesophageal fistulae	
Posterior Reversible Encephalopathy Syndrome (PRES)	
Serious infections of the skin or deeper layers under the skin	
Venous thromboembolism (VTE) *Grade 4 including pulmonary embolism*	
Other bevacizumab related toxicity	
Grade 3	Withhold until recovery to ≤ Grade 1
Grade 4	Permanent discontinuation

1. Bevacizumab should be discontinued if congestive heart failure has been newly developed or worsened after the start of the study treatment.

Note: Grade of event is based on CTCAE v.5.0. Event itself should be considered, if no grade is specified in this table.

5.4.1.2 Paclitaxel and Carboplatin

5.4.1.2.1 Re-treatment Criteria for Carboplatin and Paclitaxel

Minimum laboratory values allowed before administration for carboplatin and paclitaxel are as below:

- Hematology toxicity
    - Absolute neutrophil count: ≥ 1,500/mm^3 at the start of each cycle
    - Platelet count: ≥ 100,000/mm^3 at the start of each cycle
- Non-hematology toxicity
    - CrCl: ≥ 45 mL/min at the start of each cycle (see Appendix 11.6)
    - ≤ grade 2 at the start of each cycle (Dose modification for bevacizumab should be considered according to Section 5.4.1.1.)

Administration of carboplatin and paclitaxel can be delayed at maximum up to 3 weeks from the planned schedule. If treatment is delayed more than 3 weeks, then patient will be discontinued. Uncoupling of study treatment is not allowed until at least 4 cycles of the Induction Study Period have been completed (see Section 5.3).

5.4.1.2.2 Dose Modification and Discontinuation of Carboplatin and Paclitaxel

Based on the hematology (the lowest platelet and absolute neutrophil count) and the non-hematology toxicity from previous cycle, the dose will be modified for the subsequent cycle (Table 5-2, Table 5-3, and Table 5-4).

Table 5-2 Dose Adjustment Based on Hematologic Toxicities from the Previous Cycle

Platelets (/mm^3)	ANC (/mm^3)	Carboplatin	Paclitaxel
≥ 50,000 *and*	≥ 500	100%	100%
≥ 50,000 *and*	< 500	75%	75%
< 50,000 without bleeding *and*	Any	75%	75%
< 50,000 with bleeding from any site *and*	Any	50%	50%
Any *and*	< 1,000 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour	75%	75%

Note: The nadir (worst) value during the previous cycle should be applied.

Table 5-3 Dose Adjustment Based on Non-hematologic Toxicities from the Previous Cycle

Toxicities	Carboplatin	Paclitaxel
Grade 2 neurotoxicity – motor or sensory	100%	75%
Grade 3 or 4 neurotoxicity – motor or sensory	75%	Discontinuation
Grade 3 transaminase elevation	75%	75%
Grade 4 transaminase elevation	Discontinuation	Discontinuation
Grade 3 or 4 diarrhea	100%	75%
Grade 3 or 4 mucositis	100%	100%
Grade 3 or 4 nausea or vomiting	100%	100%
Other non-hematologic CTCAE grade 3 or 4	75%	75%

Note: The maximum (worst) grade during the previous cycle should be applied.

Table 5-4 Dose Level of Full Dose and Dose Adjustment

Dose	Carboplatin	Paclitaxel
100%	AUC 6.0	200 mg/m^2
75% reduction	• First reduction: AUC 4.5 • Second reduction: AUC 3.0	• First reduction: 150 mg/m^2 • Second reduction: 100 mg/m^2
50% reduction	• First reduction: AUC 3.0 • Second reduction: discontinuation	• First reduction: 100 mg/m^2 • Second reduction: discontinuation

Note: The adjustment of dose should be applied to the dose administered in the previous cycle.

5.4.2 Dose Escalation and Replacement

Doses which have been reduced due to toxicity must not be re-escalated. Doses missed during a treatment cycle are not to be replaced.

5.5 Overdose Management

An overdose is defined as any dose that is 10% or more than the dose prescribed. Overdose may be symptomatic or asymptomatic. Symptoms associated with an overdose must be recorded as an AE. An overdose without signs or symptoms must be documented in the study medication section of the eCRF and source documents.

5.6 Management of Clinical Supplies

5.6.1 Study Drug Packaging, Labelling, and Storage

Study drug will be packaged and labelled according to regulatory requirements.

The appropriate amount of study drug will be allocated to each patient via the IWRS or IVRS system at each visit.

A tear-off label will be attached to the vial. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Patient number/study center number
- Contents and quantity
- Lot number

- Randomization code/kit number
- Investigator's name
- Storage instructions
- Caution statement (for study use only)
- CELLTRION, Inc.'s contact name and address
- Expiry date

All study drug supplies must be stored in a secured area (e.g., a locked cabinet), protected from light. Both CT-P16 and EU-Approved Avastin must be kept at a controlled refrigerated temperature between 2°C and 8°C and it must not be frozen. The immediate containers must be kept in the outer carton until use in order to protect the study drug from light. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

5.6.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits and the tear-off label will be checked at each visit. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

The investigator agrees not to supply the study drug to any person other than subinvestigators and designated staff and agrees to administer the study drug to the patients participating in the study.

The investigator will return or destroy all investigational product according to the pharmacy manual. The investigator will destroy empty or partially used vials as well as its cartons after reconstitution per site standard operating procedure, and keep tear-off labels for accountability. This authorization may also be granted to destroy used vials immediately after administering to patients. The list of destroyed vials must be recorded.

The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc.

5.7 Blinding

This study will be double-blind (i.e., the study is blinded to both the patient and the investigator), during the Whole Study Period. The randomization codes will not be revealed to study patients, investigators, and study site personnel, except for delegated unblinded staff who will handle the study drug and pre-defined unblinded CELLTRION, Inc. and [redacted] until all final clinical data have been entered into the database and the database is locked and released for analysis.

5.7.1 Breaking the Blind

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated by knowing the study drug status of the patient. The investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS or IVRS (see study manual).

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and source documents. The medical monitor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS or IVRS to the medical monitor and the sponsor. Any patients for whom the blind is broken may continue in the study and receive the study treatment at the investigator's discretion.

[redacted]pharmacovigilance (PVG) will have access to the randomization code, if suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities.

The data safety monitoring board (DSMB) and the statistical team who provide the safety analyses for the DSMB will also be unblinded in the upon request from DSMB members during closed session.

The overall randomization code will be broken only for reporting purposes (see Section 9.6).

The unblinded team will be pre-defined before breaking the study blind. The study will remain blinded to the investigators, study site personnel except for delegated unblinded staff who will handle the study drug, patients, and pre-defined CELLTRION, Inc. and [redacted] blinded teams until all patients have completed the study and the database has been finalized for study termination.

5.8 Treatment Compliance

Patient compliance will be determined based on drug accountability as well as source documents.

5.9 Prior, Concomitant, and Subsequent Therapy

All medications used during the study, as well as all medications taken within 30 days of Day 1 of Cycle 1 in the Induction Study Period and until 28 days after the last dose of study treatment will be collected. Concomitant medications relevant to serious adverse drug reactions (ADR) that occur after the EOT visit will also be collected. For patients who do not enter the Follow-Up Period, the last assessed concomitant medication will be collected.

Concomitant medications include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. The minimum requirement is that the drug name, indication, and the dates of administration are to be recorded. Any changes in concomitant medications also will be recorded in the patient's eCRF and source documents.

Use of all medications and therapy for the treatment of nsNSCLC (e.g., surgery before enrollment or salvage treatment), from the diagnosis of disease until the last assessment date, will be recorded in the patient's eCRF and source documents. All treatments of nsNSCLC include, but are not limited to, chemotherapy, immunotherapy, targeted therapy, hormonal cancer therapy, radiation therapy, surgery, or investigational agents.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of

the investigator to ensure that details regarding the medication are recorded in full in the eCRF and source documents.

5.10 Prohibited Therapy

The following medications, treatments, or procedures during the Induction Study Period and Maintenance Study Period are prohibited:

- Anticoagulants or thrombolytic agent for therapeutic purpose (use of low dose aspirin [≤ 325mg/day] is allowed)
- Immunosuppressive agents
- Live or live attenuated vaccines
- Any concurrent anti-neoplastic therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormonal cancer therapy, radiation therapy, surgery or investigational agents for treatment of NSCLC)
- Any treatment for brain metastasis including whole brain radiotherapy, radiosurgery, or a combination of thereof.
- Herbal medications that have not received regulatory approval
- Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Bevacizumab:

- Caution should be exercised when administering bevacizumab concomitantly with medicines known to have drug interaction (e.g., zoledronic acid, risedronate, calcium carbonate/risedronate, alendronate, alendronate/cholecalciferol, pamidronate, ibandronate, etidronate, or tiludronate).

Paclitaxel:

- Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., erythromycin, fluoxetine, gemfibrozil) or induce (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

Carboplatin:

- Caution must be exercised when a patient receives aminoglycosides concomitantly.
- Vancomycin, capreomycin, and diuretics are not recommended.
- Phenytoin and fosphenytoin are not recommended.

Concomitant medication use is permitted if indicated by the Investigator for treatment of an AE.

5.11 Permitted Therapy

The following medications, treatments, or procedures during the study period are permitted.

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Colony-stimulating factors (CSFs), erythropoiesis-stimulating agents (ESAs) or leucovorin can be used for treatment of an AE. However, routine use of CSFs, ESAs or leucovorin is not permitted.

Regular concomitant use of bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to the date the informed consent form (ICF) is signed.

6 Study Assessments and Procedures

Before performing any study procedures, all potential patients and investigators will sign an ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient.

All patients will return to the study center at pre-defined time intervals for clinical assessments and blood samplings. Patients will undergo the procedures at the time points specified in the schedule of events (Table 11-1).

Disease-related information will be recorded in patients' eCRF (e.g., smoking history, TNM staging, pathological characteristics, etc.).

6.1 Pathological Diagnosis for Eligibility

The pathological diagnosis will be evaluated for confirmation of eligibility using a biopsy or cytology samples. (Table 11-1). Samples obtained before screening can be used.

Predominant nsNSCLC should be confirmed by hematoxylin and eosin staining or immunohistochemistry before randomization. Gene screening for EGFR mutation and ALK rearrangement will be also confirmed before randomization.

6.2 Efficacy Assessments

Tumor responses will be measured and recorded by using RECIST v.1.1. The primary endpoint, ORR during the Induction Study Period, and the secondary endpoint, ORR during the Whole Study Period, will be determined by the best overall response (BOR). For CR or PR, BOR must be confirmed by the subsequent assessment based on the RECIST v.1.1 (Appendix 11.2).

Efficacy assessments will be performed as per the time points specified in the schedule of events (Table 11-1).

Tumor assessment will be assessed at Screening and every 2 cycles (end of Cycle 2, Cycle 4, and Cycle 6) during the Induction Study Period and every 3 cycles (end of Cycle 3, Cycle 6, Cycle 9, Cycle 12…) during the Maintenance Study Period, and at the EOT visit. During the Follow-Up Period, it will be performed every 9 weeks until PD, death, withdrawal or start of new anti-cancer therapy if PD is not confirmed during the Induction

or Maintenance Study Periods. For screening, tumor assessment which is obtained within 4 weeks prior to Day 1 of Cycle 1 can be used as screening data for patient's convenience. These assessments should be performed within 7 days before Day 1 of the next cycle, except screening assessment.

Unequivocal malignant disease not identified before starting study drug, identified on additional tumor assessment prompted by symptoms, is considered PD and should be recorded as new lesions. If PD is uncertain, patients may continue on treatment until the next scheduled assessment or may have an unscheduled assessment earlier than this if considered appropriate by the investigator.

For a BOR of SD, measurements must have met the SD criteria at least once after start of study treatment for a minimum interval of 6 weeks (42 days or more after first administration of study drug).

At Screening, spiral CT of the chest and abdomen will be performed with a slice thickness of ≤ 5 mm. Brain CT or magnetic resonance imaging (MRI) will be performed at Screening as mandatory and will continue to be performed during the study for patients with brain metastasis at baseline. Brain metastases detected by the first brain CT or MRI must be confirmed treated and clinically stable by the subsequent brain CT or MRI before starting study treatment. Bone scans will be performed at Screening. Intravenous contrasts should be used for CT scanning.

Tumor lesions situated in a previously irradiated area are usually not considered measurable unless there has been demonstrated recurrence or progression in the lesion.

Only lesions assessed at Screening will be followed up at subsequent visits.

If disease progression/recurrence is confirmed by the investigator, the study treatment (or study drug) will be discontinued and the patients will directly enter the Follow-Up Period.

During the Induction Study Period, Maintenance Study Period, and Follow-up Period, the same methods for target and non-target lesions should be used. In addition, during the study, any method will be performed for any suspected new lesions.

Lesion details must be recorded in the eCRF and source documents in the same order as they were recorded at the Screening visit. Details of any new lesions will also be collected and recorded in the eCRF and source documents.

Response will be calculated in comparison to the baseline tumor measurements obtained before starting study treatment. Disease progression will be calculated in comparison to when the tumor burden is at a minimum. Overall response at each visit will be recorded in the eCRF and source documents.

Categorization of overall response at each visit will be based on RECIST v.1.1 using the following response categories: CR, PR, SD, PD, and inevaluable (NE) (Appendix 11.2).

In addition, all tumor assessment images will be evaluated centrally by an independent reviewer for reporting purposes for the Whole Study Period (Induction Study Period, Maintenance Study Period and Follow-Up Period). Further details regarding the independent reviewer will be described in a separate charter.

Response results by the investigator will be used to determine the eligibility and treatment practice. Tumor response evaluation will be performed as per RECIST v.1.1 and anytime based on investigator's decision.

If an unscheduled tumor assessment is performed, and the patient's disease has not progressed, the next scheduled tumor assessment will be re-calculated based on the date of last tumor assessment. However, it should be performed at the end of Cycle 6 of the Induction Study Period regardless of when the unscheduled tumor assessment is performed.

Details of the efficacy endpoints and efficacy analysis are presented in Section 7.6.1 and Section 7.6.2.

6.3 Pharmacokinetic Assessments

Pharmacokinetic samples will be collected on Day 1 of each cycle (prior to the beginning of the study drug administration [-3 days as window are allowed]) in the Induction Study Period, on Day 1 (-3 days as window are allowed) of Cycle 1 and every 3 cycles (end of Cycle 3, Cycle 6, Cycle 9...) in the Maintenance Study Period, and EOT visit. In patients whose dose is delayed from the planned schedule, serum blood samples will be obtained

on Day 22 of the last cycle (-3 days as window are allowed) (Table 11-1). Pharmacokinetic samples will be analyzed at the central laboratory.

If the blood sample is unable to be analyzed or is missing at Cycle 1, some blood samples collected for immunogenicity assessment at Cycle 1 can be used for PK assessment. Analysis will be performed at the central laboratory.

Details of the PK endpoint and PK analysis are presented in Section 7.6.3.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. Details for PK blood sampling are provided in Section 6.6.1.

6.4 Quality of Life Assessments

Quality of life will be assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ). The QLQ core 30 (QLQ-C30) and QLQ lung cancer-specific module (QLQ-LC13) will be used (see Appendix 11.5). Patients will complete the questionnaires at Screening, and every 2 cycles (end of Cycle 2, Cycle 4, and Cycle 6) of the Induction Study Period, every 3 cycles (end of Cycle 3, Cycle 6, Cycle 9…) of the Maintenance Study Period, and EOT. These assessments should be performed within 7 days before Day 1 of the next cycle, except screening assessment (Table 11-1).

6.5 Safety Assessments

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring (via vital sign and ECG), vital sign measurements (blood pressure, heart rates, respiratory rates and body temperature), weight, viral assessment, physical examination, clinical laboratory analyses, ECG, ECOG, AEs (including SAEs), adverse events of special interest (AESIs) (hypersensitivity/infusion-related reactions, gastrointestinal perforations and fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome [PRES], proteinuria, arterial thromboembolism [ATE], venous thromboembolism [VTE], hemorrhages, congestive heart failure [CHF] and ovarian failure/fertility), pregnancy testing, prior and concomitant medications throughout the study. Adverse events will be reported for term and grade according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 (Table 11-1).

6.5.1 Adverse Events

6.5.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient entered in this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after ICF was signed if any symptoms develop. Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent AE.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in either severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are clinically significant as evaluated by the investigator

Disease progression will not be used as an (S)AE(s) term. If disease progression is decided by the investigator, the patient will be discontinued from the study treatment and the disease progression will be reported in the appropriate eCRF and source documents.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

6.5.1.1.1 Adverse Events of Special Interest

The following AEs are considered AESIs, and will be reported using the same process for AEs:

- Hypersensitivity/infusion-related reactions
- Gastrointestinal perforations and fistulae
- Wound healing complications
- Hypertension
- PRES
- Proteinuria
- ATE
- VTE
- Hemorrhages
- CHF
- Ovarian failure/fertility

6.5.1.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening, that is, the patient is at risk of death at the time of the event. An event that hypothetically might have caused death if it were more severe will not be classified as an SAE.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is important medical event that may not result in death, is life threatening, or requires hospitalization when, based upon appropriate medical judgment, it may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered as SAEs. Any admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality, hospitalization solely due to progression of the underlying malignancy)
- Social admission (e.g., patient has no place to sleep)
- Purely for convenience (e.g., for easier performance of study assessments)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE

- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient

After end of the study, serious ADRs will be reported to CELLTRION, Inc. or its designee.

6.5.1.1.3 Unlisted (Unexpected) Adverse Events

An unlisted or unexpected AE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., IB) for an unapproved investigational product or the label (e.g., package insert or summary of product characteristics/US product insert) for an approved product.

6.5.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the ICF is signed until up to 28 days from last dose of study drug, regardless of the relationship to the study drug. Where an ADR (e.g., related to study drug) is ongoing at the EOT visit, the ADR will be followed until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, start of new anti-cancer therapy, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. Serious ADRs occurring during the Follow-Up Period will be reported and followed up. For patients who do not enter the Follow-Up Period, the last assessed status of AEs will be collected.

Adverse events of special interest will be closely monitored (Section 6.5.1.1.1).

At every study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over the counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF and source documents.

6.5.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF and source documents. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study treatment, time of resolution of the event, seriousness, action taken with study treatment, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs. Adverse events will be graded for severity according to the CTCAE v.5.0.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study treatment in causing or contributing to the AE will be characterized as defined in Section 6.5.1.6 and Section 6.5.1.7, respectively.

6.5.1.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.5.1.1.2) must be reported to [redacted]PVG within 24 hours from the time study center staff first learn about the event. The following contact information is to be used for SAE reporting:

[redacted]

Data entry should be completed in the eCRF and source documents by the investigator within 24 hours of awareness of an SAE. To complete the SAE report, the investigator should promptly verify and check the entered SAE in the eCRF and source documents. In the event, that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax it to [redacted] PVG within 24 hours of awareness of the event, as well as entering the SAE report into the eCRF when the system is available. If the patient is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be faxed to [redacted] PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or subinvestigator. All SAEs (regardless of relationship with the study treatment) will be followed up until satisfactory resolution or until the principal investigator or subinvestigator deems the event to be chronic or not clinically significant or the patient to be stable.

CELLTRION, Inc. or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

CELLTRION, Inc. or its designee is responsible for reporting unexpected fatal or life-threatening SUSARs (expedited reports) to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

6.5.1.5 Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the sponsor will assess the expectedness of these events using the applicable reference documents (e.g., study drug IB).

6.5.1.6 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE v.5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.5.1.7 Assessment of Causality

As discussed in Section 6.5.1.3, the investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association between an AE and the study treatment will be assessed individually for each of the study treatments administered (e.g., for CT-P16 or EU-Approved Avastin, paclitaxel, and carboplatin)

Unrelated: This relationship suggests that there is no association between the study treatment and the reported event.

Possible: This relationship suggests that treatment with the study treatment caused or contributed to the AE, e.g., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study treatment, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation or reduction of the dose of study treatment.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an AE upgrades in severity or changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in severity, it should not be reported as a new AE. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.5.2 Other Safety Assessment

6.5.2.1 Immunogenicity Testing

Immunogenicity will be assessed on Day 1 of Cycle 1 (predose), every 2 cycles (end of Cycle 2, Cycle 4, and Cycle 6) during the Induction Study Period, every 3 cycles (end of Cycle 3, Cycle 6, and Cycle 9, Cycle 12…) during the Maintenance Study Period and EOT visit. A window of -3 days before Day 1 of the next cycle are allowed during Induction Study Period and Maintenance Study Period. In the Follow-Up period, immunogenicity will be assessed once at the first visit of Follow-Up Period (9^{th} week). In patients whose dose is delayed from the planned schedule, serum blood samples will be obtained on Day 22 of the last cycle (-3 days as window are allowed) (Table 11-1).

If the blood sample is unable to be analyzed or is missing at Cycle 1, some blood samples collected for PK assessment at Cycle 1 can be used for immunogenicity assessment. Analysis will be performed at the central laboratory.

6.5.2.2 Hypersensitivity/Infusion Related Reactions Monitoring

Vital signs for hypersensitivity monitoring will be assessed before beginning the study drug infusion on Day 1 of each cycle (within 15 minutes before the beginning of the study drug infusion), at the end of study drug infusion (within 15 minutes after the end of the study drug infusion), and 60 minutes (±15 minutes) after the end of study drug infusion. In addition, ECGs (any type of lead) for hypersensitivity monitoring will be assessed at 60 minutes (±15 minutes) after the end of study drug infusion (Table 11-1).

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed.

For patients who experience or develop grade 3 or higher treatment-related hypersensitivity/infusion related reactions, study drug must be stopped immediately and the patient withdrawn from the study (Section 5.4.1.1).

Details will be recorded in both the source documents and the eCRF.

6.5.2.3 Vital Signs, Weight, and Height

Vital signs and weight measurements will be performed at the time points specified in the schedule of events (Table 11-1). Vital signs (including blood pressure, heart and respiratory rates, and temperature) will be assessed prior to study treatment administration and be measured after 5 minutes of rest (sitting). Height will be assessed at Screening only as a baseline measurement. Weight will be assessed on Day 1 of each Cycle for dose calculation. All other measurements will be documented at each study center visit. Details will be recorded in both the source documents and the eCRF.

6.5.2.4 Electrocardiogram

All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 11-1) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The investigator will then report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion.

In case of hypersensitivity, any type of ECG can be performed (Section 6.5.2.2).

6.5.2.5 Physical Examination

Physical examinations will be performed at the time points specified in the schedule of events (Table 11-1).

Physical examinations will be performed before study treatment administration.

Information about the physical examinations will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents.

6.5.2.6 Eastern Cooperative Oncology Group

Patients' ECOG performance status (Appendix 11.4) will be assessed at the time points specified in the schedule of events (Table 11-1) (*Oken et al., 1982*).

6.5.2.7 Hepatitis B, Hepatitis C, and Human Immunodeficiency Viruses

At Screening, serology tests will be performed for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody, and HIV-1 and -2 in all patients (mandatory). If the HBsAg test result is positive, the patient will be excluded from the study. If a patient is HBsAg negative, HBsAb negative or positive, and HBcAb is positive, a hepatitis B virus (HBV) DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who were enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, and HBV DNA will be performed at the end of the Induction Study Period, and the EOT visit. If the patient develops hepatitis B reactivation, the study drug must be stopped and the patient withdrawn from the study (Table 6-1). If hepatitis C antibody or HIV test result is positive, the patient will be excluded from the study.

Table 6-1 Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	HBsAb	HBcAb	HBV DNA	
+	+/-	+/-	Not applicable	Not eligible
-	+/-	+	+	Not eligible
			-	Eligible
-	+/-	-	Not applicable	Eligible

Abbreviations: DNA, deoxyribonucleic acid; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus

If a study center is not equipped to perform the specified tests, this will be discussed with the sponsor or the sponsor's designee and arrangement will be made to perform the tests centrally.

6.5.2.8 Pregnancy

Urine pregnancy test should be performed at the Screening visit (within 3 days before Day 1 of Cycle 1 of the Induction Study Period), within 3 days before Day 1 of Cycle 1 of the

Maintenance Study Period and EOT visit, or at any time if pregnancy is suspected in females of childbearing potential only. (Table 11-1).

If the urine pregnancy test gives equivocal results, a serum pregnancy test will be performed to exclude pregnant women in this study. For the Screening visit, only patients who have confirmed negative pregnancy test results will be included in this study. Pregnancy test samples will be analyzed at the local laboratory.

In an event of unexpected pregnancy during study participation and for 6 months after the last dose of study drug, patients will be counselled to inform the investigator. If a female patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to CELLTRION, Inc. and [redacted] Safety Department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug and be withdrawn from the study. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to CELLTRION, Inc. and [redacted] Safety Department within 24 hours.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained.

To prevent pregnancy, birth control methods should be used correctly and consistently from screening date to 6 months after the last study drug administration in patients and their partner of childbearing potential as below.

1. Sexual abstinence or,
2. Use of acceptable contraception

   Acceptable methods of contraception are:

   - Single method (one of following is acceptable):

     a. Intrauterine device

b. Vasectomy of a female patient's male partner

c. Contraceptive rod implanted into the skin

- Combination method (use of two of the following is required):

  a. Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

  b. Cervical cap with spermicide (nulliparous women only)

  c. Contraceptive sponge (nulliparous women only)

  d. Male condom or female condom (cannot be used together)

  e. Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin –only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

6.5.2.9 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Table 11-1). Blood samples do not need to be performed in a fasting state unless required in the opinion of the investigator.

Clinical laboratory tests for Cycle 1 of the Induction Study Period will be performed within 14 days prior to Day 1 of Cycle 1 of the Induction Study Period. Thereafter, clinical laboratory tests will be performed within 3 days prior to Day 1 of each cycle.

The following clinical laboratory analyses will be performed:

Clinical chemistry	albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatine kinase-myocardial band isoenzyme, total cholesterol, creatinine, CrCl (estimated by weight and by Cockcroft-Gault formula), gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglyceride, high-density lipoprotein cholesterol, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid
Hematology	hematocrit, hemoglobin, white blood cell count, absolute neutrophil count and platelets
Urinalysis	• bilirubin, blood, glucose, ketones, leukocytes (white blood cells), nitrite, pH, protein, specific gravity, urobilinogen and microscopic examination • 24 hour urine collection if indicated at Screening
Coagulation	Any patients who continue with low dose aspirin (≤ 325 mg/day) or any patients who have stopped regular use of aspirin (> 325 mg/day) should perform prothrombin time and prothrombin time international normalized ratio tests. • Screening • Day 1 of Cycle 1 and Cycle 2 of Induction Study Period and when clinically indicated

Clinical laboratory test samples will be analyzed at the local laboratory.

6.6 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

6.6.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments collected into serum sample tubes will be obtained before study drug administration at the time points specified in the schedule of events

(Table 11-1). All samples should be collected at the scheduled time point and the actual sampling date and time will be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained before study drug administration at the time points specified in the schedule of events (Table 11-1). All samples should be collected at the scheduled time point and the actual sampling date and time should be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 6.7.2.

6.6.3 Routine Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of events (Table 11-1).

6.7 Labelling, Storage, and Transportation of Samples

6.7.1 Sample Labelling

Each sample tube will be clearly labelled with the following information: study number, patient number, tube identification, and scheduled sampling time point.

6.7.2 Sample Storage and Shipment

Samples for PK and immunogenicity will be transferred to and analyzed in the central laboratories.

Where appropriate, the serum should be transferred into a sufficient number of transfer vials for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK and immunogenicity should be retained at the central laboratory as a backup for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK, and/or immunogenicity is not required,

the sample will be stored at CELLTRION, Inc. or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by CELLTRION, Inc. to destroy the sample. Additional tests can be conducted at CELLTRION, Inc. or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Analysis Plan

7.1 Primary Endpoint

The primary efficacy endpoint will be the ORR based on BOR during the Induction Study Period by RECIST v.1.1 (Appendix 11.2).

7.2 Secondary Endpoints

7.2.1 Efficacy Endpoints

The secondary efficacy endpoints will be the following:

- ORR based on BOR during the Whole Study Period by RECIST v.1.1 (Appendix 11.2)
- Response duration: the time between initial response (CR or PR) and PD/recurrence
- TTP: the time from randomization until PD/recurrence
- PFS: the time from randomization until PD/recurrence or death due to any cause, whichever occurs first
- OS: the time from randomization until death due to any cause

7.2.2 Pharmacokinetic Endpoints

The secondary PK endpoint is trough serum concentration.

7.2.3 Quality of Life Analyses

- QLQ-C30 and QLQ-LC13, using EORTC QLQ

7.2.4 Safety Endpoints

The secondary safety endpoints will be the following:

- Incidence and severity of AEs, including SAEs graded according to the NCI CTCAE v.5.0.

- Incidence and severity of AESIs graded according to the NCI CTCAE v.5.0.
- Immunogenicity, as assessed by the incidence of antidrug antibody and neutralized antidrug antibody.
- Vital sign measurements
- ECG
- Physical examination findings
- ECOG
- Pregnancy testing
- Clinical laboratory analyses
- Previous and concomitant medications

7.3 Sample Size Calculations

[redacted] A sample size of 305 patients per group will provide 80% power to show similarity in efficacy between CT-P16 and EU-Approved Avastin based on the expected ORR of 38% with an equivalence margin of -12.5 to 12.5 using a 95% CI (two one-sided alpha 0.025) of the difference in ORR.

Approximately 678 patients (339 in each group) will need to be enrolled for the anticipated drop-out rate of 10%.

7.4 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-treat (ITT) Population: The ITT population is defined as all patients randomly assigned to study drug, regardless of whether or not any study treatment dosing is completed. Patients will be assigned to treatment groups based on randomization.

Per-Protocol (PP) Population: The PP population is defined as all randomly assigned patients who have at least one response evaluation after receiving at least one full dose of study drug (CT-P16 or EU-Approved Avastin) in the Induction Study Period and who do not have any major protocol deviation. A major protocol deviation is one that may affect the interpretation of the primary endpoint and it will be defined in the statistical analysis plan (SAP). Final determinations of the PP population will be made at the blinded data review meeting before unblinding. Patients will be assigned to treatment groups based on randomization.

PK Population: The PK population is defined as all patients who receive at least one full dose of study drug (CT-P16 or EU-Approved Avastin) and who have at least one post treatment PK result. If any patients are found to be non-compliant with respect to dosing, a decision will be made on a case-by-case basis at the blinded data review meeting before unblinding. Patients will be assigned to treatment groups based on treatment actually received.

Safety Population: The safety population is defined as all randomly assigned patients who receive at least one dose (full or partial) of study drug (CT-P16 or EU-Approved Avastin). Patients will be assigned to treatment groups based on treatment actually received.

7.5 Description of Subgroups to be Analyzed

Subgroup analysis could be implemented to reflect medical, regulatory, regional, or ethnic considerations.

7.6 Statistical Analysis Methodology

[redacted] Continuous variables will be summarized using the descriptive statistics (the number of observations (n), mean, standard deviation, median, minimum value, and maximum value). Categorical variables will be summarized using frequency counts and percentages. Data will be listed.

Details of the statistical analyses, methods, and data conventions are described in the SAP which will be finalized before locking of the database. Changes from analyses planned in

this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.

7.6.1 Analysis of Primary Efficacy Endpoint

The similarity criterion has been set such that the confidence limits of the 95% CI of the difference in ORR will be entirely bounded by the interval (-12.5, 12.5). The primary analysis for the primary endpoint will be performed utilizing a logistic regression model considering covariates with treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect in the ITT and PP population. For primary analysis, central review result will be used. Local review result will be used as supportive data (sensitivity analysis). The resulting odds ratio and 95% CI will be converted into difference of proportions using the Delta method for the purpose of comparison. Covariates will be described in SAP.

Categorization of BOR will use the following response categories: CR, PR, SD, PD, and NE (see Appendix 11.2). For CR or PR, BOR must be confirmed by the subsequent assessment based on the RECIST v.1.1. For a BOR of SD, measurements must have met the SD criteria at least once after start of study treatment for a minimum interval of 6 weeks (42 days or more after first administration of study drug).

Objective response rate will be calculated as the number of patients with a response of CR or PR divided by the number of patients in the corresponding population. Both locally reviewed ORR and centrally reviewed ORR will be shown per treatment group and overall, including a descriptive analysis.

7.6.2 Analysis of Secondary Efficacy Endpoints

The secondary endpoint, both locally reviewed ORR and centrally reviewed ORR during the Whole Study Period, will be summarized using proportion and its corresponding 95% CI for each treatment group in the ITT and PP population.

A time-to-event analysis will be undertaken for each of the response duration, TTP, PFS, and OS in the ITT and PP population; the median time and its corresponding 95% CI for each treatment group for each secondary endpoint of time-to-event analysis will be estimated using the Kaplan-Meier method.

Response duration is defined as time from initial response (CR or PR) to determined disease progression/or recurrence.

Time to Progression is defined as time from randomization to determined disease progression/or recurrence.

Progression-free survival is defined as time from randomization to determined disease recurrence, progression or death from any cause (whichever occurs first).

For response duration, TTP, and PFS, if a patient has no event, it will be calculated censoring at the date of last adequate radiological assessment, without disease progression/or recurrence. If a patient receives another new anticancer therapy, it will be censored at the date of adequate radiological assessment, without disease progression/or recurrence, before starting another anticancer therapy. Any patient without any tumor assessment during the study will be censored at the date of randomization.

If disease progression or death is documented after missing one tumor assessment, the PFS time of these patients will be calculated assuming the event occurred on the date of progression (or death). If disease progression or death is documented after missing two or more tumor assessments, the patient will be censored for PFS at the date of their last adequate tumor assessment, without disease progression/or recurrence.

Overall survival is defined as time from randomization to death from any cause; for patients whose status is unknown, data will be censored at the time when the patient is last known to be alive.

7.6.3 Pharmacokinetic Analyses

The C_{trough} (prior to next dose) at each cycle during the Induction Study Period, and C_{trough} during the Maintenance Study Period will be analyzed. Serum concentrations will be summarized using descriptive statistics (including geometric mean and coefficient of variation [CV], as appropriate) by treatment, and study visit. Pharmacokinetic parameters will also be summarized using descriptive statistics (including geometric mean and CV, as appropriate) by treatment and study visit. All analyses will be performed based on the PK population.

7.6.4 Quality of Life Analyses

Descriptive analysis will be performed on actual score and change from baseline at each visit by treatment group in the ITT population.

7.6.5 Safety Analyses

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using MedDRA and graded for severity according to the CTCAE v.5.0. Prior and concomitant medication will be coded to drug class and PT using the World Health Organization (WHO) drug dictionary.

All safety data including immunogenicity will be listed and summarized by treatment group in the safety population.

7.6.6 Other Analyses

Demographics (age, gender, weight, height, race, ethnicity, weight loss, smoking history and lymphovascular invasion), disease-related information and medical history will be presented by means of summary tables (descriptive statistics for quantitative variables, or frequencies for qualitative variables).

7.6.7 Interim Analyses

No interim analyses are planned for this study.

7.7 Data Quality Assurance

This study will be conducted according to the ICH E6 (R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice (GCP) guidelines on quality and risk management.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff before the study, periodic monitoring visits by CELLTRION, Inc. or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRFs will be reviewed for accuracy

and completeness by the monitor during on-site monitoring visits and after their return to CELLTRION, Inc. or its designee; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from CELLTRION, Inc. or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should immediately notify CELLTRION, Inc. or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities, or the IRB/IEC.

The investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonized tripartite guideline E6 (R2): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6 (R2) guidelines shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient’s right to withdraw from the clinical study at any time without giving reasons and without jeopardizing the patient’s further course of medical treatment

- The existence of patient insurance coverage and a summary of what is included in this coverage

- Adequate time and opportunity to satisfy questions.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or subinvestigator and the patient's legal representatives (according to the local regulations) before the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator's study file. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IRB/IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRFs, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.5.1.4. In addition, the principal investigator or subinvestigator agrees to submit annual reports to his or her IRB/IEC as appropriate.

8.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor its designee is financially responsible for further testing or treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the patient's disease.

8.6 Investigator Documentation

Before beginning the study, the investigator will be asked to comply with ICH E6 (R2) 8.2 and Title 21 of the Code of Federal Regulation (CFR) by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572 or corresponding form, fully executed, and all updates on a new fully executed Form FDA 1572 or corresponding form
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572 or corresponding form. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

8.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The analytical assays will be conducted according to the general principles of the Organization for Economic Cooperation and

Development Principles of Good Laboratory Practice for testing of chemicals C(81)30(Final).

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or subinvestigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or subinvestigator agrees to maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc.

The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

The eCRFs are accessed through the appropriate system, which allows for on-site data entry and data management. Study center users can read from and write to the sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon account and password that allow for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

8.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R2) and all applicable guidelines and regulations.

8.10 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

8.11 Records Retention

All correspondence (e.g., with sponsor, IRB/IEC, or Clinical Research Associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRFs, and drug inventory sheets pertaining to the study must be kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later.

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.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the sponsor.

8.12 Patient Identification Register

The investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed by the investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

8.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the

manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

CELLTRION, Inc.
23 Academy-ro, Yeonsu-gu
Incheon, 22014, Republic of Korea
Phone: +82 32 850 5000
Fax: +82 32 850 5050
E-mail: contact@celltrion.com

Sponsor Representative

[redacted]

9.2 Vendor Contact

[redacted]

SAE Reporting

[redacted]

The names and addresses of the investigators and clinical study centers involved in the study are presented separately together with the investigators' signatures.

9.3 Monitoring

9.3.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. The DSMB will review and evaluate accumulating safety data to ensure the safety of study patients.

Further details will be provided in the independent DSMB charter.

9.3.2 Independent Tumor Review Committee

An independent tumor review committee will be used to review the tumor response for the purposes of data analysis and reporting (see Section 6.2). Full details will be provided in a separate charter.

9.3.3 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6 (R2) and current standard operating procedures.

9.3.4 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.4 Management of Protocol Amendments and Deviations

9.4.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be entered into an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from CELLTRION, Inc. or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.4.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the

investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to regulatory regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

9.5 Study Termination

Although CELLTRION, Inc. has every intention of completing the study, CELLTRION, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date of final database lock.

9.6 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports (CSRs) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of CSRs.

The sponsor plans to prepare 3 CSRs to report the following:

- To report data after completion of the Induction Study Period
- To report data up to 1-year completion of the last patient
- To report all data until the end of study.

If additional CSRs are required for regulatory or academic purposes, CSRs will be generated after the first database lock and unblinding process.

10 Reference List

American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society. 2018.

Avastin USPI (Genentech, Inc.). 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s324lbl.pdf

Barzi A and Pennell NA. Targeting Angiogenesis in Non-Small Cell Lung Cancer: Agents in Practice and Clinical Development. EJCMO 2010. 2(1):31-42.

Botrel TE et al. Efficacy of Bevacizumab (Bev) Plus Chemotherapy (CT) Compared to CT Alone in Previously Untreated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC): Systematic Review and Meta-Analysis. 2011. 74(1):89-97.

Calvert AH et al. Carboplatin Dosage: Prospective Evaluation of a Simple Formula Based on Renal Function. J Clin Oncol. 1989. 7:1748-1756.

Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976. 16(1):31-41.

Dubois D and Dubois EF. A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known. Archives of Internal Medicine. 1916. 17:863-871.

European Medicines Agency. Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/BMWP/403543/2010. 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

European Parliament and Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. DIRECTIVE 2001/20/EC. 2001. Available from:

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

Food and Drug Administration (FDA). Center for Drug Evaluation and Research (US). Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA. 2007. Available from: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

Food and Drug Administration (FDA). Center for Drug Evaluation and Research (US). Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. FDA. 2015. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf

GLOBOCAN 2012. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp. Accessed 2018.

He K et al. Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study. Clinical Cancer Research. 2016. 22(21):5167-5170.

Lim WH et al. Lean Body Mass-Adjusted Cockcroft and Gault Formula Improves the Estimation of Glomerular Filtration Rate in Subjects with Normal-Range Serum Creatinine. Nephrology (Carlton). 2006. 11(3):250-6.

Mostella RD. Simplified Calculation of Body Surface Area. New England Journal of Medicine. 1987. 317:1098.

National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 4. 2018). Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Oken et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982. 5(6):649-656.

Reck M et al. Phase III Trial of Cisplatin Plus Gemcitabine with either Placebo or Bevacizumab as First-Line Therapy for Non-Squamous Non-Small Cell Lung Cancer: AVAiL. J Clin Oncol. 2009. 27:1227-1234.

Sandler A et al. Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. N Engl J Med. 2006. 355:2542-2550.

Siegel RL et al. Cancer Statistics, 2018. CA CANCER J CLIN. 2018. 68:7-30.

SmPC Avastin®. Summary of Product Characteristics, Annex I. London: EMEA (European Medicines Agency). 2018. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf

SmPC MVASI®. Summary of Product Characteristics. EMEA (European Medicines Agency). 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/mvasi-epar-product-information_en.pdf

World Health Organization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). WHO. 2009. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf?ua

Zhang et al. Discovering and identifying New York heart association classification from electronic health records. BMC medical informatics and decision making. 2018. 18(2):48.

11 Appendices

11.1 Appendix: Schedule of Events

Table 11-1 Schedule of Events

Procedure / Cycle	Screening[1] (Day -28 to Randomization)	Induction Study Period				Maintenance Study Period[2]		EOT[3]	Follow-Up Period[4]
		Cycle 1 Day 1	Each cycle Day 1 (except Cycle 1)	End of Cycles 2 and 4	End of Cycle 6	Each Cycle Day 1	End of Cycle 3, 6, 9, 12… until PD		
Visit window (days)			±3			±3		±3	±7
Informed consent	X								
Demographics and disease-related information	X								
Medical history	X								
Gene screening[5]	X								
Inclusion and exclusion criteria[6]	X	X							
Randomization		X							
Pathological diagnosis[7]	X								
Clinical laboratory tests: hematology, clinical chemistry, urinalysis[8]	X	X	X			X		X	
Hepatitis B, C, HIV tests	X					(Cycle 1 only)		(X)	
Pregnancy test[9]	X					Cycle 1 only		X	
12-lead ECG[10]	X					Cycle 1 only		X	
Physical examination	X	X[11]	X[11]			X[11]		X	X
ECOG performance status	X	X[11]	X[11]			X[11]		X	X
Vital signs, weight and height[12]	X	X[11]	X[11]			X[11]		X	
Study drug administration		X	X			X			
Concurrent chemotherapy[13]		X	X						
Hypersensitivity monitoring		X	X			X			

Procedure / Cycle	Screening[1] (Day -28 to Randomization)	Induction Study Period				Maintenance Study Period[2]		EOT[3]	Follow-Up Period[4]
		Cycle 1 Day 1	Each cycle Day 1 (except Cycle 1)	End of Cycles 2 and 4	End of Cycle 6	Each Cycle Day 1	End of Cycle 3, 6, 9, 12… until PD		
Visit window (days)			±3			±3		±3	±7
Pharmacokinetic blood sampling[14]		X	X		X		X	X	
Tumor Evaluation[15]									
- CT (chest and abdomen)	X[16]			X	X		X	X	(X)[15]
- CT or MRI (brain)[17]	X[16]			(X)	(X)		(X)	(X)	(X)
- Bone scan[18]	X[16]			(X)	(X)		(X)	(X)	(X)
Immunogenicity[19]		X[11]		X	X		X	X	FU1 only
Quality of Life[20]	X			X	X		X	X	
Survival and further anti-cancer therapy									X
Prior/concomitant medications[21]	X								X
AEs monitoring[22]	X								X[23]

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; EOT, end of treatment; FU1, follow-up 1; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

1. Screening evaluations will be completed within 28 days prior to randomization. However, screening period can be extended to 8 weeks exclusively for treating patients who have CNS metastases before starting the study treatment and all other assessments including chest and abdomen CT scan should be completed as specified in the protocol.
2. Cycle 1 of Maintenance Study Period will occur 3 weeks after Cycle 6 of Induction Study Period. Study drug will be administered every 3 weeks until disease progression (PD) or intolerable toxicity occurrence.
3. An end of treatment (EOT) visit will occur 3 weeks after the last dose of the Induction Study Period or Maintenance Study Period regardless of the reason of discontinuation.
4. All patients will be followed every 9 weeks until death or until 36 months from Day 1 of Cycle 1 of the Induction Study Period for the last patient, whichever occurs first.
5. Gene screening results will be used for epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement.
6. The inclusion and exclusion criteria need to be confirmed prior to randomization.
7. A pathological diagnosis results will be used to confirm that the patient has non-squamous cell type.
8. Clinical laboratory tests for Cycle 1 of Induction Study Period will be performed within 14 days prior to Day 1 of Cycle 1 of the Induction Study Period. For all other cycles, clinical laboratory tests will be performed within 3 days prior to Day 1 of each cycle. Coagulation (prothrombin time, prothrombin time international

normalized ratio) test will be performed at Screening, Day 1 of Cycle 1 and Cycle 2 of Induction Study Period and when clinically indicated for the patient who has been administered aspirin. Clinical laboratory test samples will be analyzed at the local laboratory.

9. Urine pregnancy test should be performed at the Screening visit (within 3 days before Day 1 of Cycle 1), within 3 days before Day 1 of Cycle 1 of the Maintenance Study Period and EOT visit, or at any time if pregnancy is suspected in females of childbearing potential only. If the urine pregnancy test gives equivocal results, a serum pregnancy test will be performed to exclude pregnant women in this study. For the Screening visit, only patients who have confirmed negative pregnancy test results will be included in this study. Pregnancy test samples will be analyzed at the local laboratory.
10. 12-lead ECG at the Screening visit will be performed within 14 days prior to Day 1 of Cycle 1 of the Induction Study Period. For all other cycles, 12-lead ECG will be performed within 3 days prior to Day 1 of each cycle.
11. These assessments should be performed prior to study treatment administration.
12. Vital signs (including blood pressure, heart and respiratory rates, and temperature) will be assessed prior to study drug administration and be measured after 5 minutes of rest (sitting). Height will be assessed at Screening only as a baseline measurement.
13. Paclitaxel and carboplatin will be administered on Day 1 of each cycle in Induction Study Period.
14. Pharmacokinetic samples will be collected on Day 1 of each cycle (prior to the beginning of the study drug administration [-3 days as window are allowed]) in the Induction Study Period, on Day 1 (-3 days as window are allowed) of Cycle 1 and every 3 cycles (end of Cycle 3, Cycle 6, and Cycle 9...) in the Maintenance Study Period, and EOT visit. In patients whose dose is delayed from the planned schedule, serum blood samples will be obtained on Day 22 of the last cycle (-3 days as window are allowed). Pharmacokinetic samples will be analyzed at the central laboratory.
15. Tumor evaluation will be assessed at Screening and every 2 cycles during the Induction Study Period and every 3 cycles during the Maintenance Study Period, and at the EOT visit. During the Follow-Up Period, it will be performed every 9 weeks until PD, death, withdrawal or start of new anti-cancer therapy if PD is not confirmed during the Induction or Maintenance Study Periods.
16. Tumor assessment will be performed within 4 weeks before the start of study treatment.
17. Brain CT or MRI will be assessed at Screening as mandatory to assess brain metastasis. During the study, imaging will be performed for patients with brain metastasis at baseline or for any suspected new lesions.
18. Bone scans will be assessed at Screening as mandatory. During the study, scans will be performed for patients with bone metastasis at baseline or for any suspected new lesions.
19. Immunogenicity will be assessed on Day 1 of Cycle 1 (predose), every 2 cycles during the Induction Study Period, every 3 cycles during the Maintenance Study Period and EOT visit. In the Follow-Up period, immunogenicity will be assessed once at the first visit of Follow-Up Period (9^{th} week). A window of -3 days before Day 1 of the next cycle are allowed. In patients whose dose is delayed from the planned schedule, serum blood samples will be obtained on Day 22 of the last cycle (-3 days as window are allowed).
20. Quality of life should be assessed within 7 days before Day 1 of the next cycle, except screening assessment.
21. All medications used during the study, as well as all medications taken within 30 days of Day 1 of Cycle 1 in the Induction Study Period and until 28 days after the last dose of study treatment. Concomitant medications relevant to serious adverse drug reactions (ADR) occurred after the EOT visit will also be collected. For patients who do not enter the Follow-Up Period, the last assessed concomitant medications will be collected.
22. Adverse events will be assessed from the date the informed consent form is signed until up to 28 days from last dose of study drug, regardless of the relationship to the study drug. Where an ADR is ongoing at the EOT visit, the ADR will be followed until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, start of new anti-cancer therapy, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. For patients who do not enter the Follow-Up Period, the last assessed status of AEs will be collected.

23. Serious ADRs occurring during the Follow-Up Period will be reported and followed up.

11.2 Response Evaluation Criteria In Solid Tumors Version 1.1

As defined in *Eisenhauera et al., 2009*; available at
https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Key Guideline

[Definition of "Measurable" and "Non-Measurable" Lesions]

1. Measurable
   - Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by spiral CT scan (CT scan slice thickness no greater than 5 mm)
   - Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by spiral CT scan (CT scan slice thickness no greater than 5 mm)

2. Non-measurable

   All other lesions, including small lesions (longest diameter < 10 mm with spiral CT scan for non-nodal lesion or the short axis length of pathological lymph node is with 10 ≤ - < 15 mm) as well as truly non-measurable lesions including ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, etc.)

[Definition of "Target" and "Non-Target" Lesions]

1. Target lesion

   Lesion should be selected based on the largest in size and ease of measurement. Maximum of total 5 target lesions can be selected to represent the overall involved organs and maximum of 2 within one organ site.

2. Non-target lesion

   Any lesions or sites of disease not identified as target lesions.

3. New lesion

A new lesion is the appearance of any tumor independent of size clearly visible at the same anatomic location in a follow-up scan that was not present in the baseline tumor assessment.

[Definitions of Response]

Summary of RECIST v.1.1 Response Definitions for Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (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.
Stable Disease (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.
Inevaluable (NE)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline that makes comparability impossible.

Summary of RECIST v.1.1 Response Definitions for Non-Target Lesions

CR	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s)
PD	Unequivocal progression of existing non-target lesions
NE	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline that makes comparability impossible.

* The appearance of one or more new lesions, which are not present in the baseline tumor assessment is considered progression

[Overall Response at Each Assessment]

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

[Best Overall Response When Confirmation of CR and PR Required]

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR as BOR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals can be considered as 12 weeks based on each case.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after the first study drug administration at a minimum interval (6 weeks).

- The best overall response is the best response recorded from the start of the study treatment to at a subsequent time point as specified in the protocol. The best overall response can be interpreted as below table.

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

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

[a] 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 was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient 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.

11.3 American Joint Committee on Cancer Lung Cancer Staging 8th Edition

The American Joint Committee on Cancer (AJCC) Lung Cancer Staging 8th Edition is available at https://cancerstaging.org/Pages/default.aspx.

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	• Carcinoma in situ • Squamous cell carcinoma in situ (SCIS) • Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension
T1c	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤ 4 cm or if the size cannot be determined and T2b if > 4 cm, but ≤ 5 cm.
T2a	Tumor > 3 cm but ≤ 4 cm in greatest dimension

T Category	T Criteria
T2b	Tumor > 4 cm but ≤ 5 cm in greatest dimension
T3	Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor > 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Definition of Distant Metastasis (M)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
cM1b	Single extrathoracic metastasis in a single organ (including involvement of a single non-regional node)
cM1c	Multiple extrathoracic metastases in a single organ or in multiple organs

M Category	M Criteria
pM1	Distant metastasis, microscopically confirmed
pM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion, microscopically confirmed. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
pM1b	Single extrathoracic metastasis in a single organ (including involvement of a single non-regional node), microscopically confirmed
pM1c	Multiple extrathoracic metastases in a single organ or in multiple organs, microscopically confirmed

Staging

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA 1	T1mi	N0	M0
	T1a	N0	M0
IA 2	T1b	N0	M0
IA 3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

11.4 Eastern Cooperative Oncology Group Performance Status

As defined in *Oken et al., 1982*; available at http://www.ecog.org/general/perf_stat.html.

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

11.5 Quality of Life Questionnaire

11.5.1 EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

11.5.2 EORTC QLQ - LC13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

11.6 Creatinine Clearance Calculation Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from local laboratory results only.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine (Clearance for Men)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{0.81 \times \text{serum creatinine (µmol/L)}}$$

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine (Clearance for Women)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years.
[b] Weight (wt) in kilograms.
Source: *Cockcroft and Gault 1976*, *Lim et al., 2006*.

11.7 New York Heart Association Functional Classification

As defined in *Zhang et al. Discovering* and identifying New York heart association classification from electronic health records. BMC medical informatics and decision making. 2018. 18(2):48.

; available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6069768/.

The New York Heart Association (NYHA) classification is used in patients with heart failure.

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea.
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.