Clinical trial results:
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

Summary

EudraCT number	2018-002147-28
Trial protocol	PT HU BG PL HR
Global end of trial date	19 September 2023

Results information

Result version number	v1 (current)
This version publication date	07 March 2025
First version publication date	07 March 2025

Trial information

Trial identification

Sponsor protocol code	CT-P16 3.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03676192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CELLTRION, Inc.
Sponsor organisation address	23 Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of,
Public contact	CELLTRION, Inc., CELLTRION, Inc., 82 328505000, contact@celltrion.com
Scientific contact	CELLTRION, Inc., CELLTRION, Inc., 82 328505000, contact@celltrion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted according to the principles of ICH E6 (R2). The investigator conducted all aspects of this study in accordance with all national, state, and local laws or regulations.
Safety assessments were 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Belarus: 22
Country: Number of subjects enrolled	Brazil: 30
Country: Number of subjects enrolled	Chile: 23
Country: Number of subjects enrolled	Georgia: 34
Country: Number of subjects enrolled	India: 51
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Mexico: 48

Country: Number of subjects enrolled	Peru: 20
Country: Number of subjects enrolled	Russian Federation: 118
Country: Number of subjects enrolled	Serbia: 58
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Ukraine: 147
Country: Number of subjects enrolled	Viet Nam: 22
Worldwide total number of subjects	689
EEA total number of subjects	77

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	416
From 65 to 84 years	273
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 164 study centers were included in 21 countries. In these study centers, there were 1,530 screened patients and 689 randomly assigned patients to treatment. The first patient randomly assiged to treatment was 01 February 2019.

Pre-assignment

Screening details:

Patients with metastatic or recurrent non-sqamous non-small cell lung cancer were enrolled and randomly assigned in a 1:1 ratio to CT-P16 or EU-approved Avastin.

Period 1

Period 1 title	Induction Study Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P16

Arm description:

During the Induction Study Period, patients received CT-P16 every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, CT-P16 as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg intravenous (IV) of CT-P16 was be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles.

Arm title	EU-approved Avastin

Arm description:

During the Induction Study Period, patients received EU-approved Avastin every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, EU-approved Avastin as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg intravenous (IV) of EU-approved Avastin was be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles.

Number of subjects in period 1	CT-P16	EU-approved Avastin
Started	342	347
Completed	258	241
Not completed	84	106
Consent withdrawn by subject	15	20
Physician decision	3	6
Death	20	23
Progressive Disease	21	32
Adverse Events	20	21
Lost to follow-up	3	3
Protocol deviation	2	1

Period 2

Period 2 title	Maintenance Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P16

Arm description:

During the Induction Study Period, patients received CT-P16 every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, CT-P16 as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg intravenous (IV) of CT-P16 was be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles.

Arm title	EU-approved Avastin

Arm description:

During the Induction Study Period, patients received EU-approved Avastin every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, EU-approved Avastin as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Arm type	Active comparator

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg intravenous (IV) of EU-approved Avastin was be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles.

Number of subjects in period 2[1]	CT-P16	EU-approved Avastin
Started	239	227
Completed	0	0
Not completed	239	227
Consent withdrawn by subject	6	16
Physician decision	12	16
Others	9	8
Death	14	17
Progressive Disease	173	152
Adverse Events	21	16
Lost to follow-up	3	-
Protocol deviation	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 33 patients (19 patients in the CT-P16 group and 14 patients in the EU-approved Avastin treatment group) who completed the Induction Study period did not initate the Maintenance Study Period.

Baseline characteristics

Reporting groups

Reporting group title	CT-P16

Reporting group description:

During the Induction Study Period, patients received CT-P16 every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, CT-P16 as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Reporting group title	EU-approved Avastin

Reporting group description:

During the Induction Study Period, patients received EU-approved Avastin every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, EU-approved Avastin as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Reporting group values	CT-P16	EU-approved Avastin	Total
Number of subjects	342	347	689
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	203	213	416
From 65-84 years	139	134	273
85 years and over	0	0	0
Age continuous			
Units: years			
median	62	62	
full range (min-max)	32 to 82	26 to 82	-
Gender categorical			
Units: Subjects			
Female	119	125	244
Male	223	222	445

Subject analysis sets

Subject analysis set title	Intent-to-treat Population (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all randomized patients who were randomly assigned to study drug regardless of whether or not any study treatment dosing was completed. Patients were assigned to treatment groups based on randomization.

Reporting group values	Intent-to-treat Population (ITT)		
Number of subjects	689		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	416		
From 65-84 years	273		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	CT-P16

Reporting group description:

During the Induction Study Period, patients received CT-P16 every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, CT-P16 as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Reporting group title	EU-approved Avastin

Reporting group description:

During the Induction Study Period, patients received EU-approved Avastin every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, EU-approved Avastin as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Reporting group title	CT-P16

Reporting group description:

During the Induction Study Period, patients received CT-P16 every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, CT-P16 as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Reporting group title	EU-approved Avastin

Reporting group description:

During the Induction Study Period, patients received EU-approved Avastin every 3 weeks up to 6 cycles with paclitaxel and carboplatin. After the Induction Study Period, EU-approved Avastin as a monotherapy was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Subject analysis set title	Intent-to-treat Population (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all randomized patients who were randomly assigned to study drug regardless of whether or not any study treatment dosing was completed. Patients were assigned to treatment groups based on randomization.

Primary: Objective response rate during the Induction Study Period

End point title	Objective response rate during the Induction Study Period

End point description:

Tumor responses were be measured and recorded by using RECIST v.1.1. Tumor assessment were assessed at Screening and every 2 cycles (end of Cycle 2, Cycle 4, and Cycle 6) during the Induction Study Period

End point type	Primary

End point timeframe:

ORR up to Cycle 6 during the Induction Study Period

End point values	CT-P16	EU-approved Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	347		
Units: Objective response rate	145	146		

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	CT-P16 v EU-approved Avastin
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.02
upper limit	7.83

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	CT-P16

Reporting group description:

The Safety population consisted of all randomly assigned patients who received at least 1 dose (partial or full) of study drug (CT-P16 or EU-approved Avastin)

Reporting group title	EU-approved Avastin

Reporting group description:

The Safety population consisted of all randomly assigned patients who received at least 1 dose (partial or full) of study drug (CT-P16 or EU-approved Avastin)

Serious adverse events	CT-P16	EU-approved Avastin	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 345 (20.58%)	75 / 344 (21.80%)	
number of deaths (all causes)	230	236	
number of deaths resulting from adverse events	24	25	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 345 (0.87%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 345 (0.58%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Fatigue			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia malignant			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 345 (0.58%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 2	1 / 3	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anaphylactic shock			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media reaction			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			

subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal disorder			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 345 (1.45%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	4 / 345 (1.16%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	2 / 4	2 / 2	
Respiratory distress			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal nerve dysfunction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Headache			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuralgia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 345 (0.58%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 345 (1.74%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 345 (1.45%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	2 / 345 (0.58%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst rupture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	5 / 345 (1.45%)	5 / 344 (1.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 2	
Infectious pleural effusion			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	9 / 345 (2.61%)	10 / 344 (2.91%)	
occurrences causally related to treatment / all	0 / 9	2 / 10	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 345 (0.87%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Septic shock			
subjects affected / exposed	3 / 345 (0.87%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	2 / 2	1 / 2	
Urinary tract infection			
subjects affected / exposed	2 / 345 (0.58%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 345 (0.29%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 345 (0.58%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CT-P16	EU-approved Avastin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	316 / 345 (91.59%)	299 / 344 (86.92%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	24 / 345 (6.96%)	19 / 344 (5.52%)	
occurrences (all)	37	30	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 345 (6.67%)	17 / 344 (4.94%)	
occurrences (all)	35	24	
Gamma-glutamyltransferase increased			

subjects affected / exposed	22 / 345 (6.38%)	19 / 344 (5.52%)	
occurrences (all)	25	23	
Neutrophil count decreased			
subjects affected / exposed	15 / 345 (4.35%)	19 / 344 (5.52%)	
occurrences (all)	20	36	
Platelet count decreased			
subjects affected / exposed	29 / 345 (8.41%)	23 / 344 (6.69%)	
occurrences (all)	48	33	
Weight decreased			
subjects affected / exposed	34 / 345 (9.86%)	31 / 344 (9.01%)	
occurrences (all)	47	38	
Vascular disorders			
Hypertension			
subjects affected / exposed	36 / 345 (10.43%)	33 / 344 (9.59%)	
occurrences (all)	48	49	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 345 (7.25%)	20 / 344 (5.81%)	
occurrences (all)	30	28	
Neuropathy peripheral			
subjects affected / exposed	52 / 345 (15.07%)	50 / 344 (14.53%)	
occurrences (all)	67	59	
Paraesthesia			
subjects affected / exposed	35 / 345 (10.14%)	29 / 344 (8.43%)	
occurrences (all)	51	40	
Peripheral sensory neuropathy			
subjects affected / exposed	35 / 345 (10.14%)	35 / 344 (10.17%)	
occurrences (all)	46	43	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	109 / 345 (31.59%)	93 / 344 (27.03%)	
occurrences (all)	147	140	
Leukopenia			
subjects affected / exposed	30 / 345 (8.70%)	23 / 344 (6.69%)	
occurrences (all)	44	41	
Neutropenia			

subjects affected / exposed	70 / 345 (20.29%)	54 / 344 (15.70%)	
occurrences (all)	123	90	
Thrombocytopenia			
subjects affected / exposed	62 / 345 (17.97%)	48 / 344 (13.95%)	
occurrences (all)	101	77	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	63 / 345 (18.26%)	54 / 344 (15.70%)	
occurrences (all)	107	90	
Fatigue			
subjects affected / exposed	45 / 345 (13.04%)	40 / 344 (11.63%)	
occurrences (all)	75	56	
Pyrexia			
subjects affected / exposed	22 / 345 (6.38%)	17 / 344 (4.94%)	
occurrences (all)	37	26	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	38 / 345 (11.01%)	33 / 344 (9.59%)	
occurrences (all)	43	41	
Diarrhoea			
subjects affected / exposed	44 / 345 (12.75%)	47 / 344 (13.66%)	
occurrences (all)	61	64	
Nausea			
subjects affected / exposed	74 / 345 (21.45%)	64 / 344 (18.60%)	
occurrences (all)	116	99	
Vomiting			
subjects affected / exposed	30 / 345 (8.70%)	30 / 344 (8.72%)	
occurrences (all)	38	34	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 345 (4.93%)	24 / 344 (6.98%)	
occurrences (all)	21	25	
Dyspnoea			
subjects affected / exposed	23 / 345 (6.67%)	20 / 344 (5.81%)	
occurrences (all)	30	22	
Epistaxis			

subjects affected / exposed	14 / 345 (4.06%)	19 / 344 (5.52%)	
occurrences (all)	19	22	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	220 / 345 (63.77%)	218 / 344 (63.37%)	
occurrences (all)	266	261	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	44 / 345 (12.75%)	44 / 344 (12.79%)	
occurrences (all)	68	78	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 345 (10.43%)	30 / 344 (8.72%)	
occurrences (all)	73	38	
Myalgia			
subjects affected / exposed	16 / 345 (4.64%)	18 / 344 (5.23%)	
occurrences (all)	22	37	
Pain in extremity			
subjects affected / exposed	18 / 345 (5.22%)	20 / 344 (5.81%)	
occurrences (all)	35	28	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	19 / 345 (5.51%)	7 / 344 (2.03%)	
occurrences (all)	29	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 345 (12.46%)	42 / 344 (12.21%)	
occurrences (all)	56	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2019	Updated to allow 8 weeks of screening period for patients with CNS metastases to provide sufficient time for CNS treatment. Updated to clarify the prohibited therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported