Clinical trial results:
A Randomized, Open-Label Phase 2 Study Evaluating LY2875358 Plus Erlotinib and LY2875358 Monotherapy in MET Diagnostic Positive NSCLC Patients with Acquired Resistance to Erlotinib

Summary

EudraCT number	2012-005477-31
Trial protocol	DE IT GB BE ES NL FR
Global end of trial date	24 March 2016

Results information

Result version number	v1 (current)
This version publication date	10 April 2018
First version publication date	10 April 2018

Trial information

Trial identification

Sponsor protocol code	I4C-MC-JTBC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01900652
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number : 14208

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-285-4559,

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	24 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to evaluate the efficacy of the study drug known as LY2875358, administered alone or in combination with a second drug named Erlotinib, in participants affected by a defined type of lung cancer (MET biomarker diagnostic positive [≥10% of cells with 2+ or 3+ MET expression determined by immunohistochemistry (IHC)] Non-Small-Cell Lung Cancer [NSCLC]) that experienced a disease progression during the most recent treatment with Erlotinib.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	28 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	111
EEA total number of subjects	53

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)	60
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not blinded. Randomized-uncontrolled allocation method.

Arms

Are arms mutually exclusive?	Yes
Arm title	Emibetuzumab + Erlotinib

Arm description:

750 milligram (mg) Emibetuzumab flat dose given as a 1.5 hour intravenous (IV) infusion on Days 1 and 15 of a 28-day cycle and Erlotinib 150 mg given orally once daily on a 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Emibetuzumab
Investigational medicinal product code	
Other name	LY2875358
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg Emibetuzumab flat dose given as a 1.5 hour IV infusion on Days 1 and 15 of a 28-day cycle.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib 150 mg given orally once daily on a 28-day cycle.

Arm title	Emibetuzumab 750mg

Arm description:

750 mg Emibetuzumab flat dose given as a 1.5-hour IV infusion on Days 1 and 15 of a 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Emibetuzumab
Investigational medicinal product code	
Other name	LY2875358
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg Emibetuzumab flat dose given as a 1.5-hour IV infusion on Days 1 and 15 of a 28-day cycle.

Number of subjects in period 1	Emibetuzumab + Erlotinib	Emibetuzumab 750mg
Started	83	28
Post-Erlotinib Progression Tumor Sample	66 [1]	23 [2]
Completed	75	25
Not completed	8	3
Consent withdrawn by subject	1	1
Physician decision	1	1
Death	3	-
Progressive Disease	1	-
Adverse event	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subset analysis group.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subset analysis group.

Baseline characteristics

Reporting groups	
Reporting group title	Emibetuzumab + Erlotinib
Reporting group description:	
750 milligram (mg) Emibetuzumab flat dose given as a 1.5 hour intravenous (IV) infusion on Days 1 and 15 of a 28-day cycle and Erlotinib 150 mg given orally once daily on a 28-day cycle.	
Reporting group title	Emibetuzumab 750mg
Reporting group description:	
750 mg Emibetuzumab flat dose given as a 1.5-hour IV infusion on Days 1 and 15 of a 28-day cycle.	

Reporting group values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	Total
Number of subjects	83	28	111
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.2	60.9	
standard deviation	± 10.8	± 12	-
Gender categorical Units: Subjects			
Female	55	20	75
Male	28	8	36
ECOG Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death). 0 - Fully Active. 1 - Ambulatory, Restricted Strenuous Activity. 2 - Ambulatory, No Work Activities. 3 - Partially Confined to Bed, Limited Self Care. 4 - Completely Disabled. 5 - Death.			
Units: Subjects			
ECOG 0	18	9	27
ECOG 1	60	17	77
ECOG 2	5	2	7
Initial Pathological Diagnosis Units: Subjects			
Lung Adenocarcinoma	77	22	99
Squamous Cell Carcinoma	3	1	4
Large Cell Carcinoma	0	1	1
Other Subtypes of Lung Cancer	3	4	7
Ethnicity Units: Subjects			
Hispanic or Latino	4	0	4
Not Hispanic or Latino	70	21	91
Unknown or Not Reported	9	7	16
Race Units: Subjects			
Asian	10	3	13
Black or African American	4	0	4
White	64	23	87

More than One Race	1	0	1
Unknown or Not Reported	4	2	6
Region of Enrollment Units: Subjects			
Netherlands	5	5	10
Belgium	9	0	9
United States	32	9	41
Korea, Republic of	3	3	6
Italy	3	0	3
United Kingdom	6	3	9
Israel	7	4	11
France	5	2	7
Germany	4	1	5
Spain	9	1	10

Subject analysis sets

Subject analysis set title	MET-High Analysis Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with MET-High expression status (i.e ≥60% of cells with 2+ or 3+ MET expression determined by IHC) based on their post-erlotinib progression NSCLC tumor sample.

Subject analysis set title	MET-High Analysis Population (Emibetuzumab + Erlotinib)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Emibetuzumab + Erlotinib treatment arm with MET-High expression status based on their post-erlotinib progression NSCLC tumor sample.

Subject analysis set title	MET-High Analysis Population Emibetuzumab)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Emibetuzumab treatment arm with MET-High expression status based on their post-erlotinib progression NSCLC tumor sample.

Subject analysis set title	Population of Emibetuzumab
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who received Emibetuzumab on Cycle 1, Day 1, and contributed samples for analysis.

Reporting group values	MET-High Analysis Population	MET-High Analysis Population (Emibetuzumab + Erlotinib)	MET-High Analysis Population Emibetuzumab)
Number of subjects	74	53	21
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.6 ± 10.8	 ±	 ±
Gender categorical Units: Subjects			
Female	49		
Male	25		

ECOG Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death). 0 - Fully Active. 1 - Ambulatory, Restricted Strenuous Activity. 2 - Ambulatory, No Work Activities. 3 - Partially Confined to Bed, Limited Self Care. 4 - Completely Disabled. 5 - Death.			
Units: Subjects			
ECOG 0	18		
ECOG 1	49		
ECOG 2	7		
Initial Pathological Diagnosis Units: Subjects			
Lung Adenocarcinoma	66		
Squamous Cell Carcinoma	2		
Large Cell Carcinoma	4		
Other Subtypes of Lung Cancer	2		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	63		
Unknown or Not Reported	10		
Race Units: Subjects			
Asian	10		
Black or African American	3		
White	55		
More than One Race	0		
Unknown or Not Reported	6		
Region of Enrollment Units: Subjects			
Netherlands	5		
Belgium	6		
United States	30		
Korea, Republic of	4		
Italy	1		
United Kingdom	7		
Israel	7		
France	7		
Germany	1		
Spain	6		

Reporting group values	Population of Emibetuzumab		
Number of subjects	19		
Age categorical Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		

Gender categorical Units: Subjects			
Female Male			
ECOG Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death). 0 - Fully Active. 1 - Ambulatory, Restricted Strenuous Activity. 2 - Ambulatory, No Work Activities. 3 - Partially Confined to Bed, Limited Self Care. 4 - Completely Disabled. 5 - Death.			
Units: Subjects			
ECOG 0 ECOG 1 ECOG 2			
Initial Pathological Diagnosis Units: Subjects			
Lung Adenocarcinoma Squamous Cell Carcinoma Large Cell Carcinoma Other Subtypes of Lung Cancer			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race Units: Subjects			
Asian Black or African American White More than One Race Unknown or Not Reported			
Region of Enrollment Units: Subjects			
Netherlands Belgium United States Korea, Republic of Italy United Kingdom Israel France Germany Spain			

End points

End points reporting groups

Reporting group title	Emibetuzumab + Erlotinib
Reporting group description:	
750 milligram (mg) Emibetuzumab flat dose given as a 1.5 hour intravenous (IV) infusion on Days 1 and 15 of a 28-day cycle and Erlotinib 150 mg given orally once daily on a 28-day cycle.	
Reporting group title	Emibetuzumab 750mg
Reporting group description:	
750 mg Emibetuzumab flat dose given as a 1.5-hour IV infusion on Days 1 and 15 of a 28-day cycle.	
Subject analysis set title	MET-High Analysis Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with MET-High expression status (i.e ≥60% of cells with 2+ or 3+ MET expression determined by IHC) based on their post-erlotinib progression NSCLC tumor sample.	
Subject analysis set title	MET-High Analysis Population (Emibetuzumab + Erlotinib)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Emibetuzumab + Erlotinib treatment arm with MET-High expression status based on their post-erlotinib progression NSCLC tumor sample.	
Subject analysis set title	MET-High Analysis Population Emibetuzumab)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the Emibetuzumab treatment arm with MET-High expression status based on their post-erlotinib progression NSCLC tumor sample.	
Subject analysis set title	Population of Emibetuzumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received Emibetuzumab on Cycle 1, Day 1, and contributed samples for analysis.	

Primary: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point title	Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])[1]
End point description:	
ORR is confirmed best overall tumor response of CR or PR. According to RECIST v1.1, CR was defined as the disappearance of all target and non-target lesions; PR defined as a >30% decrease in the sum of the longest diameters (LD) of the target lesions, taking as reference the baseline sum of the LD. Percentage of participants was calculated as: (total number of participants with CR or PR from start of the treatment until disease progression or recurrence)/total number of participants treated) * 100. Analysis population description: All participants who are MET diagnostic positive based on the results of their post-erlotinib progression tumor sample and resistance to erlotinib.	
End point type	Primary
End point timeframe:	
Baseline to Objective Disease Progression or Start of New Anticancer Therapy (up to 15 Months)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not a comparative study; there is no p-value to report.

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	MET-High Analysis Population (Emibetuzumab + Erlotinib)	MET-High Analysis Population Emibetuzumab)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	66	23	53	21
Units: Percentage of Participants				
number (confidence interval 95%)	3 (0.4 to 10.5)	4.3 (0.1 to 21.9)	3.8 (0.5 to 13)	4.8 (0.1 to 23.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS defined as date of randomization until the date of objectively determined progression defined by Response Evaluation Criteria in Solid Tumors criteria or death from any cause, whichever is first. Progressive disease (PD) defined as ≥20% increase in sum of diameter of target lesion with the sum demonstrating an increase of ≥5 mm; appearance of ≥1 new lesions or unequivocal progression of non-target lesions. Participants with no baseline disease assessment were censored at randomization date, regardless of whether or not objectively determined PD or death was observed; participants not known to have died or to have objective progression as of data inclusion cutoff were censored at last post baseline radiological assessment date or randomization date, if there was no post baseline radiological assessment.

Analysis Population Description: All participants who are MET diagnostic positive based on results of their post-erlotinib progression tumor sample and resistance to erlotinib.

End point type	Secondary

End point timeframe:

Baseline to Objective Disease Progression or Death Due to Any Cause (Up to 24 Months).

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	23		
Units: Months				
median (confidence interval 95%)	3.3 (1.7 to 4.2)	1.6 (1.2 to 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progressive Disease

End point title	Time to Progressive Disease

End point description:

Analysis Population Description: All participants who are MET diagnostic positive based on the results of their post-erlotinib progression tumor sample and resistance to erlotinib.

End point type	Secondary

End point timeframe:

Baseline to Objective Disease Progression (up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	23		
Units: Months				
median (confidence interval 95%)	3.8 (2.7 to 4.7)	1.6 (1.4 to 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tumor Size (CTS)

End point title	Change in Tumor Size (CTS)

End point description:

Zero participants were analyzed. The number of participants with tumor reduction was not large enough for a meaningful analysis.

End point type	Secondary

End point timeframe:

Baseline to Measurement with Smallest Tumor Size (Up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage				
number (not applicable)				

Notes:

[2] - Zero participants were analyzed.

[3] - Zero participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Best Overall Disease Response of CR, PR or Stable Disease (SD) [Disease Control Rate (DCR)]

End point title	Percentage of Participants Who Achieved Best Overall Disease Response of CR, PR or Stable Disease (SD) [Disease Control Rate (DCR)]

End point description:

Participants achieved disease control if they had a best overall response of PR, CR or SD. According to RECIST v1.1, CR was the disappearance of all non-nodal target lesions, with the short axes of any target lymph node reduced to <10 mm, the disappearance of all nontarget lesions, and the normalization of tumor marker levels (if tumor markers were initially above the upper limit of normal [ULN]); PR was defined as at least a 30% decrease in the sum of the diameters of target lesions (including the short axes of any target lymph node), taking as reference the baseline sum diameter. SD was neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD, taking as reference the smallest sum diameter since treatment started. The percentage of participants who achieved disease control equals (number of participants with CR, PR, or SD)/(number of participants assessed)*100.

End point type	Secondary

End point timeframe:

Baseline to Objective Disease Progression or Participant Stops Study (24 Months)

Population description: All participants who are MET diagnostic positive based on results of their post-erlotinib progression tumor sample and resistance to erlotinib.

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	MET-High Analysis Population (Emibetuzumab + Erlotinib)	MET-High Analysis Population Emibetuzumab)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	66	23	53	21
Units: Percentage of Participants				
number (confidence interval 95%)	50 (37.4 to 62.6)	26.1 (10.2 to 48.4)	47.2 (33.3 to 61.4)	28.6 (11.3 to 52.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Zero participants were analyzed. The number of all responders (participants with CR or PR) was too small for a meaningful analysis, as there were only 4 responders.

End point type	Secondary

End point timeframe:

Date of CR or PR to Date of Objective Disease Progression or Death Due to Any Cause (up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Days				
number (not applicable)				

Notes:

[4] - Zero participants were analyzed.

[5] - Zero participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as duration from the date of study enrollment to the date of death from any cause. Participants not known to have died as of the data inclusion cut-off date were censored at the date of last contact. The last contact for participants in post-discontinuation was the last date participant was known to be alive.

Analysis Population Description: All participants who are MET diagnostic positive based on the results of their post-erlotinib progression tumor sample and resistance to erlotinib.

End point type	Secondary

End point timeframe:

Baseline to Death Due to Any Cause (up to 28 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	23		
Units: Months				
median (confidence interval 95%)	9.2 (6.7 to 12)	8.2 (3.7 to 12.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires C30 (QLQ-C30)

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires C30 (QLQ-C30)

End point description:

EORTC QLQ-C30 v3.0 is a self-administered questionnaire with multidimensional scales that measures 5 functional domains (physical, role, cognitive, emotional, and social), global health status, and symptom scales of fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea, and financial difficulties. A linear transformation is applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For functional domains and global health status, higher scores represent a better level of functioning. For symptoms scales, higher scores represented a greater degree of symptoms.

Analysis Population Description: All randomized participants with EORTC QLQ-C30 values at baseline.

End point type	Secondary

End point timeframe:

Baseline, Objective Disease Progression or Participants Stops Study (up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	MET-High Analysis Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	28	74	
Units: Units on a Scale				
number (not applicable)				
QoL	-4	-21.9	-10.2	
Physical	-11.4	-22.9	-19	
Role	-7.7	-35.4	-21	
Emotional	1.7	-13.5	-6.1	
Cognitive	-3.3	-10.4	-9.8	
Social	-12.5	-16.7	-19.8	
Fatigue	8.5	31.9	16.9	
Nausea/vomiting	-1.3	0	0.7	
Pain	1.9	14.6	2.2	
Dyspnea	9	29.2	14.5	
Insomnia	-14.1	-16.7	-15.9	
Appetite Loss	6.4	29.2	15.9	
Constipation	3.8	33.3	17.4	
Diarrhea	-5.3	4.2	-1.5	
Finance	-6.7	8.3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC Quality of Life Questionnaires Lung Cancer 13 (QLQ-LC13)

End point title	Change From Baseline in EORTC Quality of Life Questionnaires Lung Cancer 13 (QLQ-LC13)

End point description:

The EORTC lung module QLQ-LC13 comprises 13 items consisting of one multi-item scale to assess dyspnea and a series of single-item measures assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. A linear transformation is applied to standardize the raw scores to range between 0 and 100 per developer guidelines. The higher scores represent a greater degree of symptoms.

Analysis Population Description: All randomized participants with EORTC QLQ-LC13 values at baseline.

End point type	Secondary

End point timeframe:

Baseline, Objective Disease Progression or Participants Stops Study (up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	MET-High Analysis Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	83	28	74	
Units: Units on a Scale				
number (not applicable)				
Coughing	14.1	16.7	17.5	
Hemoptysis	2.6	0	3.2	
Sore Mouth	7.7	5.6	12.7	
Dysphagia	7.7	5.6	9.5	
Peripheral Neuropathy	-5.1	5.6	-4.8	
Alopecia	-5.3	0	4.8	
Pain in Chest	-1.3	5.6	1.7	
Pain in Shoulder or Arm	-2.6	0	3.2	
Pain in Other Parts	8	16.7	3.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol- 5D (EQ-5D)

End point title	Change From Baseline in EuroQol- 5D (EQ-5D)

End point description:

The EQ-5D is a generic, multidimensional, health status instrument. The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood using a 3-level scale (no problem, some problems, and major problems). These combinations of attributes were converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the Index Score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension). A negative change indicated a worsening of the participant's health status.

Additionally, patients will indicate their current health status by marking on a continuum ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

Analysis Population Description: All randomized participants with EQ-5D values at baseline.

End point type	Secondary

End point timeframe:

Baseline, Objective Disease Progression or Participants Stops Study (Up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg	MET-High Analysis Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	78	22	64	
Units: Units on a Scale (change mean)				
number (not applicable)				
Index Score	-0.1	-0.2	-0.1	
Visual Analog Scale	-8.3	-12.5	-11.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Area Under the Concentration vs Time Curve (AUC) of Emibetuzumab

End point title	Pharmacokinetics (PK): Area Under the Concentration vs Time Curve (AUC) of Emibetuzumab

End point description:

AUC(0-tlast) = area under the concentration versus time curve from time zero through the last quantifiable sample.

Analysis Population Description: All participants who received Emibetuzumab on Cycle 1, Day 1, and contributed samples for analysis.

End point type	Secondary

End point timeframe:

Cycle1 Day 1 (C1 D1): Pre-dose and End of infusion; C1 D8: Pre-dose; C1 D15, C2 D1, C2 D15, C3 D1, C3 D15, C4 D1, C4 D15: Pre-dose and End of Infusion

End point values	Population of Emibetuzumab			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Microgram*hour/milliliter (ug*hr/mL)				
geometric mean (geometric coefficient of variation)	31400 (± 75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Emibetuzumab Antibody (ADA) Response

End point title	Number of Participants with Anti-Emibetuzumab Antibody (ADA) Response

End point description:

Analysis Population Description: All participants who received at least one dose of study drug and have sufficient Anti-Emibetuzumab Antibody sample for the analysis.

End point type	Secondary

End point timeframe:

Baseline through 30-Day Follow-Up (Up to 24 Months)

End point values	Emibetuzumab + Erlotinib	Emibetuzumab 750mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	17		
Units: Participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Adverse event reporting additional description:	
I4C-MC-JTBC	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Emibetuzumab 750mg + ERLOTINIB 150mg
Reporting group description: -	
Reporting group title	Emibetuzumab 750mg
Reporting group description: -	

Serious adverse events	Emibetuzumab 750mg + ERLOTINIB 150mg	Emibetuzumab 750mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 83 (43.37%)	11 / 28 (39.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
benign neoplasm			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant neoplasm progression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
lower limb fracture			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pelvic fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax traumatic			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
toxicity to various agents			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac disorder			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericardial effusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	3 / 83 (3.61%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ascites			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 83 (3.61%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 83 (4.82%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 83 (6.02%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 83 (7.23%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
pulmonary hypertension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
stasis dermatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
hypothyroidism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteolysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pathological fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis viral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (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			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumocystis jirovecii pneumonia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
rash pustular			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (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			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal sepsis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tracheobronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Emibetuzumab 750mg + ERLOTINIB 150mg	Emibetuzumab 750mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 83 (98.80%)	28 / 28 (100.00%)	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	4 / 28 (14.29%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 83 (10.84%)	5 / 28 (17.86%)	
occurrences (all)	19	5	
axillary pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
chills			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
fatigue			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	40 / 83 (48.19%)	11 / 28 (39.29%)	
occurrences (all)	59	15	
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	5 / 83 (6.02%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
oedema peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	30 / 83 (36.14%)	9 / 28 (32.14%)	
occurrences (all)	42	15	
pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	3	
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 83 (4.82%)	4 / 28 (14.29%)	
occurrences (all)	5	4	
Reproductive system and breast disorders			
pelvic pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 83 (20.48%)	8 / 28 (28.57%)	
occurrences (all)	21	8	
dyspnoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	22 / 83 (26.51%)	8 / 28 (28.57%)	
occurrences (all)	30	11	
dyspnoea exertional			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	3	
pleural effusion			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	4 / 83 (4.82%)	3 / 28 (10.71%)	
occurrences (all)	8	3	
productive cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 83 (6.02%)	0 / 28 (0.00%)	
occurrences (all)	5	0	
pulmonary embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 83 (6.02%)	2 / 28 (7.14%)	
occurrences (all)	6	2	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	3	
insomnia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	0 / 28 (0.00%)	
occurrences (all)	7	0	
Investigations			
activated partial thromboplastin time prolonged			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 83 (7.23%)	2 / 28 (7.14%)	
occurrences (all)	8	2	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 83 (7.23%)	1 / 28 (3.57%)	
occurrences (all)	7	1	
prothrombin time prolonged			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
wound			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 83 (6.02%)	1 / 28 (3.57%)	
occurrences (all)	5	1	
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 83 (6.02%)	3 / 28 (10.71%)	
occurrences (all)	5	4	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 83 (13.25%)	3 / 28 (10.71%)	
occurrences (all)	16	3	
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 83 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
vision blurred			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Gastrointestinal disorders			

abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 83 (2.41%)	3 / 28 (10.71%)	
occurrences (all)	2	5	
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	18 / 83 (21.69%)	8 / 28 (28.57%)	
occurrences (all)	21	8	
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	21 / 83 (25.30%)	7 / 28 (25.00%)	
occurrences (all)	36	9	
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 83 (4.82%)	2 / 28 (7.14%)	
occurrences (all)	6	2	
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	27 / 83 (32.53%)	7 / 28 (25.00%)	
occurrences (all)	32	7	
stomatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 83 (10.84%)	2 / 28 (7.14%)	
occurrences (all)	11	2	
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	16 / 83 (19.28%)	6 / 28 (21.43%)	
occurrences (all)	24	8	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
dermatitis acneiform			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	15 / 83 (18.07%)	2 / 28 (7.14%)	
occurrences (all)	23	2	
dry skin			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 83 (9.64%)	2 / 28 (7.14%)	
occurrences (all)	8	2	
erythema			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
pruritus			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 83 (3.61%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
rash			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 83 (10.84%)	0 / 28 (0.00%)	
occurrences (all)	24	0	
rash maculo-papular			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 83 (7.23%)	0 / 28 (0.00%)	
occurrences (all)	8	0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 83 (9.64%)	0 / 28 (0.00%)	
occurrences (all)	13	0	
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 83 (9.64%)	1 / 28 (3.57%)	
occurrences (all)	8	3	
flank pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 83 (1.20%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
muscle spasms			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	0 / 28 (0.00%)	
occurrences (all)	7	0	
muscular weakness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 83 (1.20%)	3 / 28 (10.71%)	
occurrences (all)	3	3	
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 83 (3.61%)	3 / 28 (10.71%)	
occurrences (all)	3	5	
myalgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	1 / 28 (3.57%)	
occurrences (all)	9	1	
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	4 / 28 (14.29%)	
occurrences (all)	10	4	
Infections and infestations			
paronychia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 83 (13.25%)	0 / 28 (0.00%)	
occurrences (all)	18	0	
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 83 (7.23%)	1 / 28 (3.57%)	
occurrences (all)	10	1	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	25 / 83 (30.12%)	4 / 28 (14.29%)	
occurrences (all)	27	4	
hypoalbuminaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	13 / 83 (15.66%)	0 / 28 (0.00%)	
occurrences (all)	25	0	
hypocalcaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 83 (8.43%)	0 / 28 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported