Clinical trial results:
Phase 3, Randomized, Placebo-Controlled, Double-blind, Multi-Center, Two-Part Study of Patritumab (U3-1287) in Combination with Erlotinib in EGFR Wild-type Subjects with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Who Have Progressed on at Least One Prior Systemic Therapy

Summary

EudraCT number	2013-004371-12
Trial protocol	BE GB IT DE HU ES CZ PL
Global end of trial date	11 November 2016
Results information	
Result version number	v2 (current)
This version publication date	14 December 2017
First version publication date	26 November 2017
Version creation reason	• Correction of full data set One unclear endpoint was supposed to be deleted because the information is clearly presented in another endpoint.

Trial information

Trial identification	
Sponsor protocol code	U31287-A-U301
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02134015
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Clinical Trial Information , Daiichi Sankyo Development Limited, 44 1753 482800, euregaffairs@dsd-eu.com
Scientific contact	Clinical Trial Information , Daiichi Sankyo Development Limited, 44 1753 482800, euregaffairs@dsd-eu.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	23 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for Part A of the study is to confirm that the combination regimen of patritumab with erlotinib will improve PFS in HRG-high, EGFR-inhibitor–naïve, EGFR-wild type subjects with locally advanced or metastatic NSCLC who progressed on at least one prior systemic therapy.

The primary objective for Part B of the study is to determine if the combination regimen of patritumab with erlotinib will improve OS in EGFR-inhibitor–naïve subjects with locally advanced or metastatic, HRG-high, EGFR-wild type NSCLC who have progressed on at least one prior systemic therapy.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical \Practice (GCP), according to the ICH Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
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	United States: 26
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	145
EEA total number of subjects	117

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)	78
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was randomized on 11 Jun 2014, and the last patient's last visit occurred on 11 Nov 2016. All randomized subjects received study treatment and were included in both the Full Analysis Set and the Safety Analysis Set.

Pre-assignment

Screening details:

Of 537 patients screened, a total of 145 patients were randomized into this trial in 9 countries: United States (26 at 12 sites), Spain (19 at 5 sites), Hungary (18 at 4 sites), Italy (20 at 6 sites), Great Britain (11 at 5 sites), Poland (30 at 3 sites), Germany (16 at 6 sites), Canada (2 at 1 site) and Belgium (3 at 1 site).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Erlotinib

Arm description:

Placebo infusion every 3 weeks and oral erlotinib 150 mg/day

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

Dosage and administration details:

Placebo was administered as a continuous IV infusion

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

Dosage and administration details:

Oral erlotinib tablets 150 mg/day

Arm title	Patritumab + Erlotinib

Arm description:

Infusion of Patritumab (loading dose of 18 mg/kg, followed by 9 mg/kg every 3 weeks) and oral erlotinib 150 mg/day

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

Dosage and administration details: Infusion of Patritumab (loading dose of 18 mg/kg, followed by 9 mg/kg every 3 weeks)	
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Oral erlotinib tablets 150 mg/day	

Number of subjects in period 1	Placebo + Erlotinib	Patritumab + Erlotinib
Started	71	74
Completed	0	0
Not completed	71	74
Clinical progression	14	7
Consent withdrawn by subject	3	7
Adverse event, non-fatal	9	10
Death	2	1
Study terminated by sponsor	2	3
Progressive disease (per RECIST 1.1)	40	43
Reason not provided	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Erlotinib
Reporting group description:	
Placebo infusion every 3 weeks and oral erlotinib 150 mg/day	
Reporting group title	Patritumab + Erlotinib
Reporting group description:	
Infusion of Patritumab (loading dose of 18 mg/kg, followed by 9 mg/kg every 3 weeks) and oral erlotinib 150 mg/day	

Reporting group values	Placebo + Erlotinib	Patritumab + Erlotinib	Total
Number of subjects	71	74	145
Age categorical Units: Subjects			
Adults (18-64 years)	38	40	78
From 65-84 years	33	34	67
Age continuous Units: years			
arithmetic mean	63.3	63.9	
standard deviation	± 9.15	± 8.25	-
Gender categorical Units: Subjects			
Female	22	30	52
Male	49	44	93
Histology subtype Units: Subjects			
Adenocarcinoma	39	40	79
Squamous	28	28	56
Large cell	1	1	2
Other	3	5	8
Histology Subtype (for Randomization)			
NOS=not otherwise specified			
Units: Subjects			
Adenocarcinoma	38	40	78
Squamous-cell carcinoma/NOS	33	34	67
ECOG Score			
ECOG=Eastern Cooperative Oncology Group			
Units: Subjects			
0 - Fully Active	24	25	49
1 - Restricted in Physically Strenuous Activity	47	49	96
HRG Expression from IXRS			
HRG=heregulin; IXRS=Interactive Web/Voice Response System			
Units: Subjects			
High	48	47	95
Low	23	27	50

End points

End points reporting groups

Reporting group title	Placebo + Erlotinib
Reporting group description:	
Placebo infusion every 3 weeks and oral erlotinib 150 mg/day	
Reporting group title	Patritumab + Erlotinib
Reporting group description:	
Infusion of Patritumab (loading dose of 18 mg/kg, followed by 9 mg/kg every 3 weeks) and oral erlotinib 150 mg/day	

Primary: Part A: Progression Free Survival (PFS) in Heregulin-high Patients

End point title	Part A: Progression Free Survival (PFS) in Heregulin-high Patients[1]

End point description:

PFS is defined as the time from the date of randomization to the earlier of the dates of first objective documentation of radiographic disease progression (as per RECIST Version 1.1 per investigator assessment) or death resulting from any cause.

Kaplan-Meier Estimate. Confidence interval (CI) for median was computed using the Brookmeyer-Crowley method.

End point type	Primary

End point timeframe:

by trial termination (at 20 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: 80% confidence interval is included in the data table.

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	47		
Units: months				
number (confidence interval 80%)	2.7 (1.7 to 2.9)	1.9 (1.4 to 3.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Part A: PFS in Heregulin-low Patients

End point title	Part A: PFS in Heregulin-low Patients[2]

End point description:

PFS is defined as the time from the date of randomization to the earlier of the dates of first objective documentation of radiographic disease progression (as per RECIST Version 1.1 per investigator assessment) or death resulting from any cause.

Kaplan-Meier Estimate. Confidence interval (CI) for median was computed using the Brookmeyer-Crowley method.

End point type	Primary

End point timeframe:

by trial termination (at 20 months)

Notes:

[2] - 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: 80% confidence interval is included in the data table.

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	27		
Units: Months				
number (confidence interval 80%)	2.8 (1.4 to 4.2)	1.5 (1.4 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Primary Endpoint Overall Survival

End point title	Part B: Primary Endpoint Overall Survival[3]

End point description:

No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.

End point type	Primary

End point timeframe:

Various Timepoints

Notes:

[3] - 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: There were no subjects analyzed because the trial was terminated at the end of Part A.

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Percentage of patients				
number (not applicable)				

Notes:

[4] - No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.
[5] - No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Key secondary efficacy endpoint: Overall Survival

End point title	Part A: Key secondary efficacy endpoint: Overall Survival

End point description:

Percentage of participants who survived for the length of the trial

End point type	Secondary

End point timeframe:
during Part A

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	74		
Units: Percentage of participants				
number (not applicable)				
HRG High (n=48, 47)	31.3	36.2		
HRG Low (n=23,27)	30.4	29.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Key secondary efficacy endpoints: PFS; TTD

End point title	Part B: Key secondary efficacy endpoints: PFS; TTD

End point description:
No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.

End point type	Secondary

End point timeframe:
Various timepoints

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Percentage of patients				
number (not applicable)				

Notes:
[6] - No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.
[7] - No patients were analyzed in Part B endpoints because the trial was terminated at the end of Part A.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Key secondary efficacy endpoint: Objective Response Rate (ORR)

End point title	Part A: Key secondary efficacy endpoint: Objective Response Rate (ORR)

End point description:
Objective response is defined as complete response or partial response

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo + Erlotinib	Patritumab + Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	74		
Units: Percentage of patients				
number (confidence interval 80%)				
HRG High (n=48,47)	6.3 (2.4 to 13.7)	2.2 (0.2 to 8.6)		
HRG Low (n=23,27)	13.6 (5.3 to 28.6)	3.7 (0.4 to 14.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

53 days after the last dose of patritumab/placebo or 30 days after the last dose of erlotinib, whichever is later

Adverse event reporting additional description:

Treatment emergent (TE) adverse events (AEs) are reported for patritumab only. If relatedness is missing, the AE is counted as related to patritumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo+Erlotinib

Reporting group description:

Placebo infusion every 3 weeks and oral erlotinib 150 mg/day

Reporting group title	Patritumab+Erlotinib

Reporting group description:

Infusion of Patritumab (loading dose of 18 mg/kg, followed by 9 mg/kg every 3 weeks) and oral erlotinib 150 mg/day

Serious adverse events	Placebo+Erlotinib	Patritumab+Erlotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 71 (40.85%)	27 / 74 (36.49%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (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			

subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 71 (1.41%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 71 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 71 (1.41%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydropneumothorax			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (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	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 71 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphagia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin fissures			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
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	1 / 71 (1.41%)	0 / 74 (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			
Pneumonia			
subjects affected / exposed	3 / 71 (4.23%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Empyema			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcal sepsis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo+Erlotinib	Patritumab+Erlotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 71 (92.96%)	68 / 74 (91.89%)	
Investigations			
Weight decreased			
subjects affected / exposed	8 / 71 (11.27%)	10 / 74 (13.51%)	
occurrences (all)	9	11	
Vascular disorders			
Pruritus			
subjects affected / exposed	4 / 71 (5.63%)	6 / 74 (8.11%)	
occurrences (all)	6	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 71 (7.04%)	0 / 74 (0.00%)	
occurrences (all)	5	0	
Dysgeusia			
subjects affected / exposed	3 / 71 (4.23%)	4 / 74 (5.41%)	
occurrences (all)	3	4	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	17 / 71 (23.94%)	11 / 74 (14.86%)	
occurrences (all)	23	12	
Oedema peripheral			
subjects affected / exposed	6 / 71 (8.45%)	5 / 74 (6.76%)	
occurrences (all)	6	5	
Asthenia			
subjects affected / exposed	5 / 71 (7.04%)	5 / 74 (6.76%)	
occurrences (all)	6	5	
Chest pain			
subjects affected / exposed	4 / 71 (5.63%)	2 / 74 (2.70%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 71 (5.63%)	6 / 74 (8.11%)	
occurrences (all)	5	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 71 (30.99%)	39 / 74 (52.70%)	
occurrences (all)	41	62	
Nausea			
subjects affected / exposed	16 / 71 (22.54%)	15 / 74 (20.27%)	
occurrences (all)	18	19	
Stomatitis			
subjects affected / exposed	2 / 71 (2.82%)	11 / 74 (14.86%)	
occurrences (all)	2	18	
Vomiting			
subjects affected / exposed	7 / 71 (9.86%)	10 / 74 (13.51%)	
occurrences (all)	8	13	
Constipation			
subjects affected / exposed	2 / 71 (2.82%)	9 / 74 (12.16%)	
occurrences (all)	2	9	
Dyspepsia			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	
occurrences (all)	3	7	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	16 / 71 (22.54%)	9 / 74 (12.16%)	
occurrences (all)	21	11	
Cough			
subjects affected / exposed	11 / 71 (15.49%)	10 / 74 (13.51%)	
occurrences (all)	11	14	
Haemoptysis			
subjects affected / exposed	5 / 71 (7.04%)	5 / 74 (6.76%)	
occurrences (all)	7	7	
Dysphonia			
subjects affected / exposed	0 / 71 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	26 / 71 (36.62%)	28 / 74 (37.84%)	
occurrences (all)	46	57	
Dermatitis acneiform			
subjects affected / exposed	6 / 71 (8.45%)	13 / 74 (17.57%)	
occurrences (all)	7	23	
Dry skin			
subjects affected / exposed	7 / 71 (9.86%)	13 / 74 (17.57%)	
occurrences (all)	7	14	
Alopecia			
subjects affected / exposed	3 / 71 (4.23%)	6 / 74 (8.11%)	
occurrences (all)	4	6	
Rash maculo-papular			
subjects affected / exposed	4 / 71 (5.63%)	3 / 74 (4.05%)	
occurrences (all)	4	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 71 (4.23%)	4 / 74 (5.41%)	
occurrences (all)	3	4	
Infections and infestations			
Paronychia			
subjects affected / exposed	3 / 71 (4.23%)	7 / 74 (9.46%)	
occurrences (all)	4	16	
Rhinitis			

subjects affected / exposed	0 / 71 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 71 (18.31%)	17 / 74 (22.97%)	
occurrences (all)	16	21	
Hypomagnesaemia			
subjects affected / exposed	4 / 71 (5.63%)	7 / 74 (9.46%)	
occurrences (all)	7	17	
Hypokalaemia			
subjects affected / exposed	1 / 71 (1.41%)	6 / 74 (8.11%)	
occurrences (all)	1	6	
Dehydration			
subjects affected / exposed	1 / 71 (1.41%)	4 / 74 (5.41%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2014	The protocol was modified to clarify packaging and safety requirements, to describe new assessments and time windows, and correct footnotes and formatting.
12 May 2015	The study design was modified to create a smaller, more efficient Part A, designed to focus upon efficacy in the high HRG subgroup, for which the primary objective is part of this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Since there was an unplanned follow up with a patient on 11 Nov 2016, the global end of trial date is actually later than previously reported to health authorities (18-May-2016). The actual global end of trial date is 11-November-2016.

Notes: