



Clinical trial results:

A Randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab (MetMAB) in Combination with Tarceva® (Erlotinib) in Patients with MET Diagnostic-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Standard Chemotherapy for Advanced or Metastatic Disease.

Summary

EudraCT number	2011-002224-40
Trial protocol	BE ES DE HU IE NL GB IT PL
Global end of trial date	28 January 2016

Results information

Result version number	v1 (current)
This version publication date	07 July 2016
First version publication date	07 July 2016

Trial information

Trial identification

Sponsor protocol code	OAM4971g
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01456325
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, global.trial_information@roche.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	14 March 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine whether the combination of onartuzumab + erlotinib was superior (in terms of overall survival [OS]) to placebo + erlotinib after standard platinum-based chemotherapy in participants with MET diagnostic-positive NSCLC.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2012
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	Croatia: 2
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Ukraine: 4

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	United States: 164
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Chile: 4
Worldwide total number of subjects	499
EEA total number of subjects	196

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)	295
From 65 to 84 years	204
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Second and third-line NSCLC participants with at least 1 prior platinum based line of therapy, were tested for MET status and endothelial growth factor receptor (EGFR) mutation status, and MET diagnostic positive participants were randomized in 1:1 ratio to either "onartuzumab+erlotinib" or "placebo+erlotinib".

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, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Onartuzumab+Erlotinib

Arm description:

Participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally once daily (QD) from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	RO5490258
Other name	MetMab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received onartuzumab 15 mg/kg IV infusion on Day 1 of every 3-week cycle.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received erlotinib 150 mg tablet orally once daily from Day 1, Cycle 1.

Arm title	Placebo+Erlotinib
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Arm description:

Participants received onartuzumab matching placebo on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally QD from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

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

Dosage and administration details:

Participants received onartuzumab matching placebo on Day 1 of every 3-week cycle.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received erlotinib 150 mg tablet orally once daily from Day 1, Cycle 1.

Number of subjects in period 1	Onartuzumab+Erlotinib	Placebo+Erlotinib
Started	250	249
Completed	0	0
Not completed	250	249
Disease progression	2	-
Consent withdrawn by subject	13	10
Disease progression	-	5
Death	185	180
Unspecified	1	2
Sponsor decision	44	50
Lost to follow-up	4	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Onartuzumab+Erlotinib
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Reporting group description:

Participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally once daily (QD) from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Erlotinib
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Reporting group description:

Participants received onartuzumab matching placebo on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally QD from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group values	Onartuzumab+Erlotinib	Placebo+Erlotinib	Total
Number of subjects	250	249	499
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	61.4 ± 10	61.5 ± 10.2	-
Gender categorical Units: Subjects			
Female	111	110	221
Male	139	139	278

End points

End points reporting groups

Reporting group title	Onartuzumab+Erlotinib
Reporting group description:	
Participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally once daily (QD) from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.	
Reporting group title	Placebo+Erlotinib
Reporting group description:	
Participants received onartuzumab matching placebo on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg tablet orally QD from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time from date of randomization until death from any cause. OS was estimated using Kaplan-Meier method and 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT population was considered for analysis of this end point.	
End point type	Primary
End point timeframe:	
Randomization until death (up to approximately 18 months) (assessed at the treating physician's discretion using the local standard-of-care practice)	

End point values	Onartuzumab+Erlotinib	Placebo+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: months				
median (confidence interval 95%)	6.8 (6.1 to 7.5)	9.1 (7.7 to 10.2)		

Statistical analyses

Statistical analysis title	Stratified analysis
Statistical analysis description:	
Strata were: MET immunohistochemistry (IHC) clinical score (2+ versus [vs] 3+), prior lines of therapy (1 vs. 2), histology (non-squamous vs. squamous), and endothelial growth factor receptor (EGFR)-activating mutation status (yes vs. no). Hazard ratios were estimated by Cox regression.	
Comparison groups	Placebo+Erlotinib v Onartuzumab+Erlotinib

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0677
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.65

Secondary: Percentage of Participants With Disease Progression or Death

End point title	Percentage of Participants With Disease Progression or Death
End point description:	
<p>Progressive disease (PD) was determined based on investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version (V) 1.1. PD: At least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). The appearance of one or more new lesions is also considered progression. ITT population was considered for analysis of this end point.</p>	
End point type	Secondary
End point timeframe:	
<p>Randomization until disease progression or death, whichever occurred first (up to approximately 18 months) (assessed at the treating physician's discretion using the local standard-of-care practice)</p>	

End point values	Onartuzumab+ Erlotinib	Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: percentage of participants				
number (not applicable)	84	81.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
<p>PFS was defined as the time between the date of randomization and the date of the first documented disease progression or death, whichever occurred first. Progressive disease (PD): At least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. Kaplan-Meier estimates were used for analysis. ITT population was considered for analysis</p>	

of this end point.

End point type	Secondary
End point timeframe:	
Randomization until disease progression or death, whichever occurred first (up to approximately 18 months) (assessed at the treating physician's discretion using the local standard-of-care practice)	

End point values	Onartuzumab+ Erlotinib	Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: months				
median (confidence interval 95%)	2.7 (2.4 to 2.9)	2.6 (1.5 to 2.8)		

Statistical analyses

Statistical analysis title	Stratified analysis
Statistical analysis description:	
Strata were: Met IHC clinical score (2+ vs. 3+), prior lines of therapy (1 vs. 2), histology (nonsquamous vs. squamous), and EGFR activating mutation status (yes vs. no). Hazard ratios were estimated by Cox regression.	
Comparison groups	Onartuzumab+Erlotinib v Placebo+Erlotinib
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9249
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.2

Secondary: Percentage of Participants with an Objective Response Assessed Using RECIST V 1.1

End point title	Percentage of Participants with an Objective Response Assessed Using RECIST V 1.1
End point description:	
Objective response is defined as a complete response (CR) or partial response (PR). Participants without a post-baseline tumor assessment are considered as non-responders. CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population was considered for analysis of this end point.	
End point type	Secondary

End point timeframe:

Randomization until disease progression or death, whichever occurred first (up to approximately 18

End point values	Onartuzumab+ Erlotinib	Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: percentage of participants				
number (confidence interval 95%)	8.4 (5.27 to 12.55)	9.6 (6.27 to 14)		

Statistical analyses

Statistical analysis title	Statistical analysis I
Comparison groups	Onartuzumab+Erlotinib v Placebo+Erlotinib
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6295
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rates
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.26
upper limit	3.79

Secondary: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13) Scores

End point title	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13) Scores
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End point description:

EORTC QLQ-LC13: consisted of 13 questions with one symptom scale for dyspnea of 3 items and 10 single items (cough, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm/shoulder, other pain, pain medication). Questions used 4-point scale (1 'Not at all' to 4 'Very much'). Scores were averaged and transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms. Number of subjects analyzed = number of participants evaluable for this end point and "n" represents number of participants evaluable at the specified time point for the specified symptom scale. When n=0, the mean±standard deviation was reported as 99999±99999; when n=1, the upper confidence interval was reported as "99999" as it is not estimable.

End point type	Secondary
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End point timeframe:

Screening, Day 1 of Cycles 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 (cycle length = 21 days), study drug discontinuation visit (up to approximately 18 months)

End point values	Onartuzumab+ Erlotinib	Placebo+ Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	241		
Units: units on a scale				
arithmetic mean (standard deviation)				
Screening: Alopecia (n=237,240)	18 (± 31.5)	18.9 (± 32.3)		
Screening: Coughing (n=238,237)	35.6 (± 26.8)	38.3 (± 27.1)		
Screening: Dysphagia (n=237,240)	7.7 (± 18.9)	6.9 (± 16.1)		
Screening: Dyspnoea (n=237,241)	27.3 (± 23.3)	27.9 (± 23.3)		
Screening: Haemoptysis (n=236,241)	3.7 (± 12.9)	3.7 (± 12.9)		
Screening: Pain in arm/shoulder (n=238,241)	16.9 (± 27)	19.4 (± 28.3)		
Screening: Pain in chest (n=237,241)	19.8 (± 27.7)	15.1 (± 25.5)		
Screening: Pain in other parts (n=234,238)	28.9 (± 33.3)	27.9 (± 31.6)		
Screening: Peripheral neuropathy (n=238,241)	22.8 (± 28.7)	18.7 (± 28)		
Screening: Sore mouth (n=236,241)	6.6 (± 18.4)	5 (± 15.6)		
Cycle 2 Day 1: Alopecia (n=196,205)	8.3 (± 22.2)	9.9 (± 23.7)		
Cycle 2 Day 1: Coughing (n=197,206)	30.5 (± 23.8)	33.3 (± 27.5)		
Cycle 2 Day 1: Dysphagia (n=198,205)	8.6 (± 19.9)	8.8 (± 19.8)		
Cycle 2 Day 1: Dyspnoea (n=197,206)	28.8 (± 23.1)	26.9 (± 21)		
Cycle 2 Day 1: Haemoptysis (n=197,206)	3.6 (± 10.3)	3.4 (± 12.5)		
Cycle 2 Day 1: Pain in Arm/Shoulder (n=197,204)	14.6 (± 23.6)	15.8 (± 28)		
Cycle 2 Day 1: Pain in chest (n=195,206)	13.2 (± 22.3)	12.3 (± 21.3)		
Cycle 2 Day 1: Pain in other parts (n=190,205)	28.9 (± 30.4)	28.6 (± 32.9)		
Cycle 2 Day 1: Peripheral neuropathy (n=196,206)	26.4 (± 30.8)	19.6 (± 29.3)		
Cycle 2 Day 1: Sore mouth (n=198,206)	17.7 (± 28)	14.6 (± 24.5)		
Cycle 4 Day 1: Alopecia (n=116,110)	11.2 (± 22.4)	12.1 (± 22)		
Cycle 4 Day 1: Coughing (n=118,111)	30.5 (± 26)	27.6 (± 23.3)		
Cycle 4 Day 1: Dysphagia (n=116,111)	6.6 (± 15.4)	7.2 (± 18.8)		
Cycle 4 Day 1: Dyspnoea (n=117,111)	25.9 (± 21.8)	24.6 (± 19.3)		
Cycle 4 Day 1: Haemoptysis (n=118,111)	1.7 (± 7.4)	2.4 (± 9.8)		
Cycle 4 Day 1: Pain in Arm/Shoulder (n=118,111)	18.6 (± 26.3)	13.2 (± 23.9)		
Cycle 4 Day 1: Pain in chest (n=118,110)	14.4 (± 22)	10.6 (± 18)		
Cycle 4 Day 1: Pain in other parts (n=117,111)	28.5 (± 31)	22.2 (± 27.8)		
Cycle 4 Day 1: Peripheral neuropathy (n=118,111)	27.7 (± 30.3)	19.8 (± 26.7)		
Cycle 4 Day 1: Sore mouth (n=118,111)	12.7 (± 21.3)	10.5 (± 22.5)		
Cycle 6 Day 1: Alopecia (n=76,77)	16.7 (± 28.5)	17.3 (± 26.3)		
Cycle 6 Day 1: Coughing (n=76,77)	28.9 (± 26.3)	32 (± 22.6)		

Cycle 6 Day 1: Dysphagia (n=77,78)	7.4 (± 19.2)	4.3 (± 12.4)		
Cycle 6 Day 1: Dyspnoea (n=77,78)	29.5 (± 23.1)	22.6 (± 18.7)		
Cycle 6 Day 1: Haemoptysis (n=77,78)	4.8 (± 14)	4.3 (± 12.4)		
Cycle 6 Day 1: Pain in Arm/Shoulder (n=77,77)	20.8 (± 28.1)	9.1 (± 19.2)		
Cycle 6 Day 1: Pain in chest (n=77,78)	17.3 (± 22.7)	11.5 (± 20)		
Cycle 6 Day 1: Pain in other parts (n=75,75)	24 (± 28.8)	23.1 (± 28.5)		
Cycle 6 Day 1: Peripheral neuropathy (n=76,78)	26.3 (± 31.9)	23.9 (± 27.9)		
Cycle 6 Day 1: Sore mouth (n=76,78)	14.5 (± 22.7)	8.1 (± 16.3)		
Cycle 8 Day 1: Alopecia (n=41,54)	13.8 (± 24.7)	13 (± 25.4)		
Cycle 8 Day 1: Coughing (n=41,53)	25.2 (± 20.8)	29.6 (± 25)		
Cycle 8 Day 1: Dysphagia (n=41,54)	9.8 (± 18.6)	5.6 (± 14.1)		
Cycle 8 Day 1: Dyspnoea (n=41,53)	25.7 (± 21.4)	19.5 (± 18.7)		
Cycle 8 Day 1: Haemoptysis (n=41,54)	1.6 (± 7.3)	4.3 (± 13)		
Cycle 8 Day 1: Pain in Arm/Shoulder (n=40,54)	18.3 (± 28.2)	11.7 (± 21.6)		
Cycle 8 Day 1: Pain in chest (n=41,54)	17.9 (± 24.8)	8 (± 17.1)		
Cycle 8 Day 1: Pain in other parts (n=40,54)	25 (± 32.7)	22.2 (± 28.2)		
Cycle 8 Day 1: Peripheral neuropathy (n=40,53)	26.7 (± 32.2)	18.9 (± 24)		
Cycle 8 Day 1: Sore mouth (n=41,54)	4.9 (± 11.9)	7.4 (± 14)		
Cycle 10 Day 1: Alopecia (n=26,34)	11.5 (± 24.8)	16.7 (± 27.5)		
Cycle 10 Day 1: Coughing (n=27,34)	18.5 (± 16.9)	25.5 (± 18.5)		
Cycle 10 Day 1: Dysphagia (n=27,34)	7.4 (± 14.1)	3.9 (± 10.9)		
Cycle 10 Day 1: Dyspnoea (n=27,34)	23.3 (± 16.7)	18.6 (± 17)		
Cycle 10 Day 1: Haemoptysis (n=27,34)	0 (± 0)	1 (± 5.7)		
Cycle 10 Day 1: Pain in Arm/Shoulder (n=27,33)	7.4 (± 16.9)	16.2 (± 29)		
Cycle 10 Day 1: Pain in chest (n=27,34)	13.6 (± 24.9)	6.9 (± 16)		
Cycle 10 Day 1: Pain in other parts (n=27,32)	30.9 (± 35.7)	18.8 (± 23.9)		
Cycle 10 Day 1: Peripheral neuropathy (n=27,34)	24.7 (± 32.8)	18.6 (± 24.9)		
Cycle 10 Day 1: Sore mouth (n=27,34)	11.1 (± 18.5)	6.9 (± 13.7)		
Cycle 12 Day 1: Alopecia (n=17,22)	7.8 (± 25.1)	12.1 (± 26.3)		
Cycle 12 Day 1: Coughing (n=17,22)	11.8 (± 20.2)	30.3 (± 28.9)		
Cycle 12 Day 1: Dysphagia (n=17,22)	3.9 (± 11.1)	1.5 (± 7.1)		
Cycle 12 Day 1: Dyspnoea (n=17,22)	15.7 (± 13.1)	14.6 (± 17.3)		
Cycle 12 Day 1: Haemoptysis (n=17,22)	0 (± 0)	1.5 (± 7.1)		
Cycle 12 Day 1: Pain in Arm/Shoulder (n=17,22)	19.6 (± 26.5)	19.7 (± 24.5)		
Cycle 12 Day 1: Pain in chest (n=17,21)	7.8 (± 14.6)	7.9 (± 18)		
Cycle 12 Day 1: Pain in other parts (n=16,22)	22.9 (± 29.1)	19.7 (± 26.5)		
Cycle 12 Day 1: Peripheral neuropathy (n=17,22)	23.5 (± 32.8)	19.7 (± 24.5)		
Cycle 12 Day 1: Sore mouth (n=17,22)	9.8 (± 19.6)	3 (± 9.8)		
Cycle 14 Day 1: Alopecia (n=9,10)	14.8 (± 33.8)	16.7 (± 23.6)		
Cycle 14 Day 1: Coughing (n=9,10)	18.5 (± 24.2)	26.7 (± 21.1)		
Cycle 14 Day 1: Dysphagia (n=9,10)	7.4 (± 14.7)	6.7 (± 14.1)		
Cycle 14 Day 1: Dyspnoea (n=9,10)	22.2 (± 17.6)	27.8 (± 27.8)		
Cycle 14 Day 1: Haemoptysis (n=9,10)	0 (± 0)	6.7 (± 21.1)		

Cycle 14 Day 1: Pain in Arm/Shoulder (n=9,10)	22.2 (± 16.7)	16.7 (± 23.6)		
Cycle 14 Day 1: Pain in chest (n=9,10)	3.7 (± 11.1)	13.3 (± 23.3)		
Cycle 14 Day 1: Pain in other parts (n=9,9)	33.3 (± 28.9)	14.8 (± 24.2)		
Cycle 14 Day 1: Peripheral neuropathy (n=9,10)	40.7 (± 36.4)	16.7 (± 23.6)		
Cycle 14 Day 1: Sore mouth (n=9,10)	7.4 (± 14.7)	10 (± 22.5)		
Cycle 16 Day 1: Alopecia (n=4,5)	16.7 (± 33.3)	20 (± 29.8)		
Cycle 16 Day 1: Coughing (n=4,5)	16.7 (± 19.2)	26.7 (± 14.9)		
Cycle 16 Day 1: Dysphagia (n=4,5)	0 (± 0)	20 (± 18.3)		
Cycle 16 Day 1: Dyspnoea (n=4,5)	22.2 (± 18.1)	24.4 (± 12.2)		
Cycle 16 Day 1: Haemoptysis (n=4,5)	0 (± 0)	13.3 (± 18.3)		
Cycle 16 Day 1: Pain in Arm/Shoulder (n=3,5)	11.1 (± 19.2)	13.3 (± 18.3)		
Cycle 16 Day 1: Pain in chest (n=4,5)	0 (± 0)	13.3 (± 18.3)		
Cycle 16 Day 1: Pain in other parts (n=3,5)	66.7 (± 57.7)	20 (± 29.8)		
Cycle 16 Day 1: Peripheral neuropathy (n=4,5)	66.7 (± 38.5)	0 (± 0)		
Cycle 16 Day 1: Sore mouth (n=4,5)	25 (± 16.7)	0 (± 0)		
Cycle 18 Day 1: Alopecia (n=0,3)	99999 (± 99999)	11.1 (± 19.2)		
Cycle 18 Day 1: Coughing (n=0,3)	99999 (± 99999)	22.2 (± 19.2)		
Cycle 18 Day 1: Dysphagia (n=0,3)	99999 (± 99999)	11.1 (± 19.2)		
Cycle 18 Day 1: Dyspnoea (n=0,3)	99999 (± 99999)	25.9 (± 23.1)		
Cycle 18 Day 1: Haemoptysis (n=0,3)	99999 (± 99999)	11.1 (± 19.2)		
Cycle 18 Day 1: Pain in Arm/Shoulder (n=0,3)	99999 (± 99999)	11.1 (± 19.2)		
Cycle 18 Day 1: Pain in chest (n=0,3)	99999 (± 99999)	0 (± 0)		
Cycle 18 Day 1: Pain in other parts (n=0,3)	99999 (± 99999)	0 (± 0)		
Cycle 18 Day 1: Peripheral neuropathy (n=0,3)	99999 (± 99999)	0 (± 0)		
Cycle 18 Day 1: Sore mouth (n=0,3)	99999 (± 99999)	11.1 (± 19.2)		
Cycle 20 Day 1: Alopecia (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 20 Day 1: Coughing (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 20 Day 1: Dysphagia (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 20 Day 1: Dyspnoea (n=0,1)	99999 (± 99999)	44.4 (± 99999)		
Cycle 20 Day 1: Haemoptysis (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 20 Day 1: Pain in Arm/Shoulder (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 20 Day 1: Pain in chest (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 20 Day 1: Pain in other parts (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 20 Day 1: Peripheral neuropathy (n=0,1)	99999 (± 99999)	0 (± 99999)		

Cycle 20 Day 1: Sore mouth (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 22 Day 1: Alopecia (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 22 Day 1: Coughing (n=0,1)	99999 (± 99999)	66.7 (± 99999)		
Cycle 22 Day 1: Dysphagia (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 22 Day 1: Dyspnoea (n=0,1)	99999 (± 99999)	44.4 (± 99999)		
Cycle 22 Day 1: Haemoptysis (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Cycle 22 Day 1: Pain in Arm/Shoulder (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 22 Day 1: Pain in chest (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 22 Day 1: Pain in other parts (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 22 Day 1: Peripheral neuropathy (n=0,1)	99999 (± 99999)	0 (± 99999)		
Cycle 22 Day 1: Sore mouth (n=0,1)	99999 (± 99999)	33.3 (± 99999)		
Drug discontinuation (DD): Alopecia (n=132,137)	18.7 (± 30.1)	10.9 (± 22.5)		
DD: Coughing (n=132,137)	38.1 (± 26.7)	42.6 (± 31)		
DD: Dysphagia (n=130,137)	14.1 (± 26.2)	11.4 (± 22.3)		
DD: Dyspnoea (n=131,136)	39.5 (± 25.6)	35.7 (± 27.7)		
DD: Haemoptysis (n=132,137)	5.1 (± 15.1)	4.9 (± 16.9)		
DD: Pain in Arm/Shoulder (n=131,137)	20.1 (± 28.8)	21.9 (± 30.1)		
DD: Pain in chest (n=132,137)	21.7 (± 29.1)	19 (± 26.8)		
DD: Pain in other parts (n=130,134)	35.1 (± 34.8)	31.6 (± 34)		
DD: Peripheral neuropathy (n=131,137)	25.4 (± 28.6)	17 (± 26.5)		
DD: Sore mouth (n=132,136)	12.1 (± 24.5)	12.5 (± 21.1)		
Unscheduled (Uns): Alopecia (n=6,1)	11.1 (± 17.2)	0 (± 99999)		
Uns: Coughing (n=6,1)	44.4 (± 27.2)	33.3 (± 99999)		
Uns: Dysphagia (n=6,1)	22.2 (± 17.2)	0 (± 99999)		
Uns: Dyspnoea (n=6,1)	33.3 (± 25.3)	55.6 (± 99999)		
Uns: Haemoptysis (n=6,1)	0 (± 0)	33.3 (± 99999)		
Uns: Pain in Arm/Shoulder (n=6,1)	27.8 (± 25.1)	33.3 (± 99999)		
Uns: Pain in chest (n=6,1)	22.2 (± 27.2)	0 (± 99999)		
Uns: Pain in other parts (n=5,1)	33.3 (± 33.3)	66.7 (± 99999)		
Uns: Peripheral neuropathy (n=6,1)	44.4 (± 45.5)	33.3 (± 99999)		
Uns: Sore mouth (n=6,1)	11.1 (± 17.2)	0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Onartuzumab Serum Concentrations

End point title	Onartuzumab Serum Concentrations ^[1]
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End point description:

C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1; C4D1=Cycle 4 Day 1. Number of subjects analyzed=number of participants evaluable for this end point. "n" represents number of participants evaluable at the specified time point. When data was not available, the mean (standard deviation) was

reported as 99999±99999.

End point type	Secondary
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End point timeframe:

1 hour pre-onartuzumab (Pr-O) infusion on Day 1 of Cycles 1, 2, and 4, 1 hour post-onartuzumab (Po-O) infusion on Day 1 of Cycle 1 (cycle length = 21 days and duration of infusion = 60 minutes), End of treatment (up to approximately 18 months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Onartuzumab serum concentration assessment is applicable only in "Onartuzumab + Erlotinib" and only this arm is selected.

End point values	Onartuzumab+ Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	240			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
C1D1: 1 hour Pr-O (n=240)	99999 (± 99999)			
C1D1: 1 hour Po-O (n=235)	382 (± 201)			
C2D1: 1 hour Pr-O (n=202)	36.2 (± 13.9)			
C4D1: 1 hour Po-O (n=125)	62 (± 28.6)			
End of treatment (n=137)	43.1 (± 32.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 20 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo+Erlotinib
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Reporting group description:

Participants received onartuzumab matching placebo on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg orally QD from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Onartuzumab+Erlotinib
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Reporting group description:

Participants received onartuzumab 15 mg/kg IV infusion on Day 1 of every cycle of 3 weeks along with erlotinib 150 mg orally QD from Day 1, Cycle 1 until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Serious adverse events	Placebo+Erlotinib	Onartuzumab+Erlotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 244 (33.20%)	89 / 248 (35.89%)	
number of deaths (all causes)	11	17	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (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 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Arterial occlusive disease			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 244 (0.82%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose ulceration			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (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			
Asthenia			
subjects affected / exposed	0 / 244 (0.00%)	4 / 248 (1.61%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 244 (0.82%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema			
subjects affected / exposed	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	2 / 244 (0.82%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 244 (1.64%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 244 (0.41%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 244 (0.82%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 244 (2.05%)	6 / 248 (2.42%)	
occurrences causally related to treatment / all	1 / 7	2 / 6	
deaths causally related to treatment / all	1 / 2	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 244 (1.23%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	2 / 244 (0.82%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 244 (0.82%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 244 (0.41%)	5 / 248 (2.02%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 244 (0.82%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 244 (0.00%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 244 (1.23%)	8 / 248 (3.23%)	
occurrences causally related to treatment / all	1 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 4	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (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	2 / 244 (0.82%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 244 (0.41%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cardiac output decreased			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 244 (0.41%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 244 (0.41%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac tamponade			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 244 (0.82%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	4 / 244 (1.64%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 244 (0.82%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 244 (0.41%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 244 (0.82%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticular perforation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	4 / 244 (1.64%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal perforation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	5 / 244 (2.05%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 244 (0.82%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 244 (0.41%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	2 / 244 (0.82%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 244 (0.41%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 244 (0.82%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	

Nephrolithiasis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
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			
Arthralgia			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 244 (0.00%)	4 / 248 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
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	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain			
subjects affected / exposed	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute endocarditis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			

subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 244 (4.10%)	7 / 248 (2.82%)	
occurrences causally related to treatment / all	0 / 10	2 / 7	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pulmonary sepsis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
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	0 / 244 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Scrotal abscess			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (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	1 / 244 (0.41%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 244 (0.41%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 244 (1.23%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 244 (0.82%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 244 (0.41%)	4 / 248 (1.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	1 / 244 (0.41%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 244 (0.00%)	1 / 248 (0.40%)	
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	Placebo+Erlotinib	Onartuzumab+Erlotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	225 / 244 (92.21%)	228 / 248 (91.94%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 244 (3.69%)	19 / 248 (7.66%)	
occurrences (all)	10	22	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 244 (2.46%)	18 / 248 (7.26%)	
occurrences (all)	6	24	
Blood bilirubin increased			
subjects affected / exposed	13 / 244 (5.33%)	4 / 248 (1.61%)	
occurrences (all)	14	4	
Weight decreased			
subjects affected / exposed	32 / 244 (13.11%)	18 / 248 (7.26%)	
occurrences (all)	32	19	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 244 (4.51%)	19 / 248 (7.66%)	
occurrences (all)	11	22	
Dysgeusia			
subjects affected / exposed	16 / 244 (6.56%)	17 / 248 (6.85%)	
occurrences (all)	16	17	
Headache			

subjects affected / exposed occurrences (all)	5 / 244 (2.05%) 5	15 / 248 (6.05%) 16	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	22 / 244 (9.02%) 28	18 / 248 (7.26%) 21	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	23 / 244 (9.43%) 24	24 / 248 (9.68%) 29	
Chest pain subjects affected / exposed occurrences (all)	14 / 244 (5.74%) 16	15 / 248 (6.05%) 15	
Fatigue subjects affected / exposed occurrences (all)	76 / 244 (31.15%) 89	69 / 248 (27.82%) 80	
Mucosal inflammation subjects affected / exposed occurrences (all)	12 / 244 (4.92%) 12	16 / 248 (6.45%) 16	
Oedema peripheral subjects affected / exposed occurrences (all)	20 / 244 (8.20%) 22	59 / 248 (23.79%) 73	
Pyrexia subjects affected / exposed occurrences (all)	27 / 244 (11.07%) 29	17 / 248 (6.85%) 19	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	10 / 244 (4.10%) 10	17 / 248 (6.85%) 21	
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 244 (5.74%) 14	13 / 248 (5.24%) 16	
Constipation subjects affected / exposed occurrences (all)	34 / 244 (13.93%) 40	30 / 248 (12.10%) 32	
Diarrhoea			

subjects affected / exposed	116 / 244 (47.54%)	100 / 248 (40.32%)	
occurrences (all)	169	149	
Nausea			
subjects affected / exposed	62 / 244 (25.41%)	68 / 248 (27.42%)	
occurrences (all)	73	88	
Stomatitis			
subjects affected / exposed	23 / 244 (9.43%)	23 / 248 (9.27%)	
occurrences (all)	27	28	
Vomiting			
subjects affected / exposed	37 / 244 (15.16%)	38 / 248 (15.32%)	
occurrences (all)	46	53	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 244 (22.54%)	36 / 248 (14.52%)	
occurrences (all)	57	39	
Dyspnoea			
subjects affected / exposed	49 / 244 (20.08%)	51 / 248 (20.56%)	
occurrences (all)	54	59	
Epistaxis			
subjects affected / exposed	12 / 244 (4.92%)	18 / 248 (7.26%)	
occurrences (all)	12	18	
Haemoptysis			
subjects affected / exposed	18 / 244 (7.38%)	13 / 248 (5.24%)	
occurrences (all)	24	14	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 244 (5.74%)	9 / 248 (3.63%)	
occurrences (all)	14	9	
Dermatitis acneiform			
subjects affected / exposed	64 / 244 (26.23%)	79 / 248 (31.85%)	
occurrences (all)	75	104	
Dry skin			
subjects affected / exposed	53 / 244 (21.72%)	51 / 248 (20.56%)	
occurrences (all)	55	63	
Pruritus			

subjects affected / exposed occurrences (all)	32 / 244 (13.11%) 43	30 / 248 (12.10%) 37	
Rash subjects affected / exposed occurrences (all)	92 / 244 (37.70%) 116	95 / 248 (38.31%) 126	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	7 / 244 (2.87%) 7	14 / 248 (5.65%) 14	
Insomnia subjects affected / exposed occurrences (all)	18 / 244 (7.38%) 21	22 / 248 (8.87%) 23	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	18 / 244 (7.38%) 19	28 / 248 (11.29%) 33	
Muscle spasms subjects affected / exposed occurrences (all)	9 / 244 (3.69%) 9	16 / 248 (6.45%) 22	
Muscular weakness subjects affected / exposed occurrences (all)	6 / 244 (2.46%) 7	14 / 248 (5.65%) 18	
Pain in extremity subjects affected / exposed occurrences (all)	12 / 244 (4.92%) 14	16 / 248 (6.45%) 18	
Infections and infestations Paronychia subjects affected / exposed occurrences (all)	25 / 244 (10.25%) 34	27 / 248 (10.89%) 27	
Urinary tract infection subjects affected / exposed occurrences (all)	13 / 244 (5.33%) 17	8 / 248 (3.23%) 10	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	78 / 244 (31.97%) 91	72 / 248 (29.03%) 80	

Dehydration			
subjects affected / exposed	16 / 244 (6.56%)	10 / 248 (4.03%)	
occurrences (all)	19	12	
Hypoalbuminaemia			
subjects affected / exposed	10 / 244 (4.10%)	43 / 248 (17.34%)	
occurrences (all)	10	46	
Hypokalaemia			
subjects affected / exposed	16 / 244 (6.56%)	16 / 248 (6.45%)	
occurrences (all)	20	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2012	A futility boundary was added to the interim analysis, allowing for early termination of the trial if it became clear that a statistically significant difference by the end of study would be improbable. The total number of events for the final analysis was revised to 364 (from 363) and the number of participants was revised to 490 (from 480). The analysis of the secondary efficacy endpoints was revised from a two-sided 5% significance level to a one-sided 2.5% significance level. Per a request made by the European Voluntary Harmonization Procedure, it was added that vital signs to be collected at baseline and each subsequent visit, and regular urinalysis was also added. Procedures for potential emergency unblinding were included. The use of systemic corticosteroids was added for the treatment of chronic obstructive pulmonary disease.
22 May 2014	The protocol was amended after the protocol-specified interim analysis for efficacy and futility was performed. This interim analysis demonstrated that participants in the onartuzumab arm did not have longer OS (primary endpoint), longer PFS (secondary endpoint), or an improved objective response rate (ORR) compared with participants in the placebo arm. This amendment reduced the protocol-specified assessments for participants who were either on active study treatment (onartuzumab arm or erlotinib alone) or in the survival follow-up period. Additionally, the end of study was defined, and the potential provision for drug supply through a program-wide independent protocol was included to allow participants from this and other onartuzumab studies to continue receiving treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 January 2016	A decision was made by the sponsor to discontinue further clinical development of onartuzumab.	-

Notes:

Limitations and caveats

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

The clinical development of onartuzumab was terminated as per decision made by sponsor primarily due to limited efficacy observed in the conduct of this study and was not based on safety-related issues.

Notes: