



Clinical trial results:

A Phase III, Multicenter, Placebo-Controlled, Double-Blind, Randomized Clinical Trial to Evaluate the Efficacy of Bevacizumab in Combination With Tarceva (Erlotinib) Compared With Erlotinib Alone for Treatment of Advanced Non-Small Cell Lung Cancer (NscLc) After Failure of Standard First-Line Chemotherapy

Summary

EudraCT number	2006-006626-26
Trial protocol	DE BE BG SE IT
Global end of trial date	23 December 2019

Results information

Result version number	v1 (current)
This version publication date	03 January 2021
First version publication date	03 January 2021

Trial information

Trial identification

Sponsor protocol code	OSI3364g
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00130728
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, 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	23 December 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of the combination of bevacizumab with Tarceva (erlotinib) in relation to Tarceva monotherapy in participants receiving second-line therapy for non-small cell lung cancer.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United States: 576
Worldwide total number of subjects	636
EEA total number of subjects	29

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)	309
From 65 to 84 years	327
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

636 participants were enrolled at 177 sites worldwide

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
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Arm title	erlotinib HCl + bevacizumab
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Arm description:

Oral erlotinib HCl 150 mg/day orally + intravenous infusion of bevacizumab at a dose of 15 mg/kg on the first day of each 3-week cycle

Arm type	Experimental
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A 15 milligram (mg)/kilogram (kg) dose of bevacizumab was administered on the first day of each 3-week cycle.

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

Dosage and administration details:

Erlotinib was administered as a 150 mg dose daily.

Arm title	erlotinib HCl + placebo
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Arm description:

Oral erlotinib HCl 150 mg/day orally + intravenous infusion of placebo at a dose of 15 mg/kg on the first day of each 3-week cycle

Arm type	Placebo
Investigational medicinal product name	erlotinib HCl
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib was administered as a 150 mg dose daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A 15 mg/kg dose of placebo was administered on the first day of each 3-week cycle.

Number of subjects in period 1	erlotinib HCl + bevacizumab	erlotinib HCl + placebo
Started	319	317
Completed	57	57
Not completed	262	260
Consent withdrawn by subject	-	2
Death	258	258
Lost to follow-up	4	-

Baseline characteristics

Reporting groups

Reporting group title	erlotinib HCl + bevacizumab
Reporting group description: Oral erlotinib HCl 150 mg/day orally + intravenous infusion of bevacizumab at a dose of 15 mg/kg on the first day of each 3-week cycle	
Reporting group title	erlotinib HCl + placebo
Reporting group description: Oral erlotinib HCl 150 mg/day orally + intravenous infusion of placebo at a dose of 15 mg/kg on the first day of each 3-week cycle	

Reporting group values	erlotinib HCl + bevacizumab	erlotinib HCl + placebo	Total
Number of subjects	319	317	636
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-59 years)	91	90	181
From 60-64 years	62	66	128
From 65-69 years	59	53	112
>= 70 years	107	108	215
Age Continuous Units: years			
arithmetic mean	64.8	65.0	-
standard deviation	± 10.4	± 10.3	-
Gender Categorical Units: Subjects			
Female	148	147	295
Male	171	170	341
Race/Ethnicity Units: Subjects			
White	264	257	521
Black	21	33	54
Asian or Pacific Islander	23	18	41
Hispanic	10	8	18
American Indian or Alaskan Native	0	1	1
Other	1	0	1

End points

End points reporting groups

Reporting group title	erlotinib HCl + bevacizumab
Reporting group description: Oral erlotinib HCl 150 mg/day orally + intravenous infusion of bevacizumab at a dose of 15 mg/kg on the first day of each 3-week cycle	
Reporting group title	erlotinib HCl + placebo
Reporting group description: Oral erlotinib HCl 150 mg/day orally + intravenous infusion of placebo at a dose of 15 mg/kg on the first day of each 3-week cycle	

Primary: Overall survival (OS) among all randomized patients

End point title	Overall survival (OS) among all randomized patients
End point description: Overall Survival was defined as the period from the date of randomization until the date of patient death from any cause. For patients who had not died, survival data was censored at the date of last contact.	
End point type	Primary
End point timeframe: From the date of randomization until the date of patient death from any cause, or the date of last contact. (Up to 3.1 years)	

End point values	erlotinib HCl + bevacizumab	erlotinib HCl + placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	317		
Units: Months				
median (confidence interval 95%)	9.3 (7.39 to 11.47)	9.2 (7.85 to 11.60)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	erlotinib HCl + bevacizumab v erlotinib HCl + placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7583 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.799
upper limit	1.177

Notes:

[1] - relative to placebo arm

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

PFS was defined as the time from randomization to documented disease progression, as determined by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), or death on study treatment, whichever occurred first.

End point type	Secondary
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End point timeframe:

From randomization to documented disease progression or death on study treatment, whichever occurred first. (Up to 3.1 years)

End point values	erlotinib HCl + bevacizumab	erlotinib HCl + placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	317		
Units: Months				
median (confidence interval 95%)	3.4 (2.79 to 4.27)	1.7 (1.48 to 2.53)		

Statistical analyses

Statistical analysis title	Progression-Free Survival
Comparison groups	erlotinib HCl + bevacizumab v erlotinib HCl + placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.519
upper limit	0.748

Notes:

[2] - relative to placebo arm

Secondary: Percentage of Participants with Objective Response

End point title	Percentage of Participants with Objective Response
End point description:	
Objective response was defined as a complete or partial response determined by RECIST on two consecutive occasions ≥ 4 weeks apart.	
End point type	Secondary
End point timeframe:	
The median duration of Objective response was up to 9.7 months	

End point values	erlotinib HCl + bevacizumab	erlotinib HCl + placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	306		
Units: Percentage of participants				
number (confidence interval 95%)	12.6 (9.1 to 16.8)	6.2 (3.8 to 9.5)		

Statistical analyses

Statistical analysis title	Objective Response
Comparison groups	erlotinib HCl + bevacizumab v erlotinib HCl + placebo
Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068 ^[3]
Method	Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	11.3

Notes:

[3] - relative to placebo arm

Secondary: Duration of objective response

End point title	Duration of objective response
End point description:	
Duration of objective response was defined as the period from the date of the initial partial or complete response until the date of disease progression or death on study treatment from any cause. For patients who had not died, data was censored at the date of last contact.	
End point type	Secondary
End point timeframe:	
Period from Objective response until disease progression or death on study treatment. (Up to 29.5 months)	

End point values	erlotinib HCl + bevacizumab	erlotinib HCl + placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Months				
median (confidence interval 95%)	9.7 (6.90 to 19.48)	8.4 (3.48 to 14.88)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to up to 3.8 years (for Adverse Events) From randomization until last patient last visit or 14.5 years from start of study (for Serious Adverse Events)

Adverse event reporting additional description:

Safety analyses were based on safety-evaluable randomized participants.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	erlotinib HCl + placebo
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Reporting group description:

Oral erlotinib HCl 150 mg/day orally + intravenous infusion of placebo at a dose of 15 mg/kg on the first day of each 3-week cycle

Reporting group title	erlotinib HCl + bevacizumab
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Reporting group description:

Oral erlotinib HCl 150 mg/day orally + intravenous infusion of bevacizumab at a dose of 15 mg/kg on the first day of each 3-week cycle

Serious adverse events	erlotinib HCl + placebo	erlotinib HCl + bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	121 / 313 (38.66%)	146 / 313 (46.65%)	
number of deaths (all causes)	258	258	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Pleural Effusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (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	6 / 313 (1.92%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	3 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular Vein Thrombosis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 313 (0.00%)	4 / 313 (1.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trousseau's Syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis Limb			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Venous Thrombosis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	2 / 313 (0.64%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Influenza Like Illness			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	4 / 313 (1.28%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 313 (0.96%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Food Allergy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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			
Bronchial Obstruction			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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	0 / 313 (0.00%)	6 / 313 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnoea			
subjects affected / exposed	24 / 313 (7.67%)	12 / 313 (3.83%)	
occurrences causally related to treatment / all	1 / 24	1 / 12	
deaths causally related to treatment / all	2 / 2	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydropneumothorax			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	4 / 313 (1.28%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea at Rest			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	5 / 313 (1.60%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	2 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	8 / 313 (2.56%)	12 / 313 (3.83%)	
occurrences causally related to treatment / all	3 / 8	9 / 12	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pneumonitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural Effusion			
subjects affected / exposed	9 / 313 (2.88%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pulmonary Haemorrhage			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary Oedema			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory Failure			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Congestion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood Culture Positive			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Rate Increased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 313 (0.96%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip Fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Retinopathy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal Injury			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Wound Dehiscence			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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	0 / 313 (0.00%)	4 / 313 (1.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Angina Pectoris			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			

subjects affected / exposed	4 / 313 (1.28%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			

subjects affected / exposed	0 / 313 (0.00%)	5 / 313 (1.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhage Intracranial			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Pressure Increased			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible Posterior Leukoencephalopathy Syndrome			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic Encephalopathy			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Paralysis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness Unilateral			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision Blurred			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 313 (1.28%)	7 / 313 (2.24%)	
occurrences causally related to treatment / all	3 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	1 / 1	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis Erosive			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			

subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Perforation			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia, Obstructive			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large Intestine Perforation			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Obstruction			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Perforation			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Stenosis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			

subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	4 / 313 (1.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 313 (1.28%)	3 / 313 (0.96%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 313 (0.32%)	6 / 313 (1.92%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hiatus Hernia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Exfoliative Rash			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Ulcer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	5 / 313 (1.60%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal Pain			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
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	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast Cellulitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 313 (0.32%)	4 / 313 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	3 / 313 (0.96%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung Infection			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal Abscess			

subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 313 (3.19%)	15 / 313 (4.79%)	
occurrences causally related to treatment / all	1 / 11	2 / 16	
deaths causally related to treatment / all	4 / 4	2 / 2	
Pyelonephritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (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 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 313 (0.64%)	4 / 313 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to Thrive			

subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 313 (0.96%)	7 / 313 (2.24%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (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	erlotinib HCl + placebo	erlotinib HCl + bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	306 / 313 (97.76%)	310 / 313 (99.04%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 313 (8.31%)	77 / 313 (24.60%)	
occurrences (all)	27	79	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	23 / 313 (7.35%)	33 / 313 (10.54%)	
occurrences (all)	26	36	
Fatigue			
subjects affected / exposed	124 / 313 (39.62%)	146 / 313 (46.65%)	
occurrences (all)	125	147	
Chest Pain			
subjects affected / exposed	24 / 313 (7.67%)	27 / 313 (8.63%)	
occurrences (all)	25	29	
Asthenia			
subjects affected / exposed	20 / 313 (6.39%)	34 / 313 (10.86%)	
occurrences (all)	22	36	
Oedema Peripheral			
subjects affected / exposed	32 / 313 (10.22%)	18 / 313 (5.75%)	
occurrences (all)	34	18	
Mucosal Inflammation			
subjects affected / exposed	16 / 313 (5.11%)	35 / 313 (11.18%)	
occurrences (all)	16	35	
Pain			
subjects affected / exposed	18 / 313 (5.75%)	15 / 313 (4.79%)	
occurrences (all)	21	17	
Chills			
subjects affected / exposed	11 / 313 (3.51%)	23 / 313 (7.35%)	
occurrences (all)	11	23	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	76 / 313 (24.28%)	73 / 313 (23.32%)	
occurrences (all)	77	73	
Dyspnoea			
subjects affected / exposed	64 / 313 (20.45%)	61 / 313 (19.49%)	
occurrences (all)	80	70	
Epistaxis			
subjects affected / exposed	30 / 313 (9.58%)	63 / 313 (20.13%)	
occurrences (all)	31	63	
Dysphonia			

subjects affected / exposed occurrences (all)	6 / 313 (1.92%) 6	33 / 313 (10.54%) 34	
Pharyngolaryngeal Pain subjects affected / exposed occurrences (all)	14 / 313 (4.47%) 14	27 / 313 (8.63%) 27	
Haemoptysis subjects affected / exposed occurrences (all)	14 / 313 (4.47%) 16	22 / 313 (7.03%) 24	
Wheezing subjects affected / exposed occurrences (all)	9 / 313 (2.88%) 10	17 / 313 (5.43%) 19	
Dyspnoea Exertional subjects affected / exposed occurrences (all)	17 / 313 (5.43%) 17	6 / 313 (1.92%) 6	
Rhinorrhoea subjects affected / exposed occurrences (all)	6 / 313 (1.92%) 6	16 / 313 (5.11%) 16	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	25 / 313 (7.99%) 26	38 / 313 (12.14%) 39	
Anxiety subjects affected / exposed occurrences (all)	30 / 313 (9.58%) 32	26 / 313 (8.31%) 26	
Depression subjects affected / exposed occurrences (all)	19 / 313 (6.07%) 20	31 / 313 (9.90%) 31	
Investigations Weight Decreased subjects affected / exposed occurrences (all)	41 / 313 (13.10%) 41	65 / 313 (20.77%) 65	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	28 / 313 (8.95%) 28	53 / 313 (16.93%) 55	
Dizziness			

subjects affected / exposed occurrences (all)	31 / 313 (9.90%) 31	41 / 313 (13.10%) 41	
Dysgeusia subjects affected / exposed occurrences (all)	19 / 313 (6.07%) 19	29 / 313 (9.27%) 29	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	29 / 313 (9.27%) 30	19 / 313 (6.07%) 20	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	162 / 313 (51.76%) 162	203 / 313 (64.86%) 206	
Nausea subjects affected / exposed occurrences (all)	99 / 313 (31.63%) 101	121 / 313 (38.66%) 121	
Constipation subjects affected / exposed occurrences (all)	45 / 313 (14.38%) 45	49 / 313 (15.65%) 50	
Vomiting subjects affected / exposed occurrences (all)	49 / 313 (15.65%) 52	57 / 313 (18.21%) 61	
Stomatitis subjects affected / exposed occurrences (all)	27 / 313 (8.63%) 27	40 / 313 (12.78%) 40	
Abdominal Pain subjects affected / exposed occurrences (all)	25 / 313 (7.99%) 26	29 / 313 (9.27%) 32	
Dyspepsia subjects affected / exposed occurrences (all)	16 / 313 (5.11%) 17	21 / 313 (6.71%) 22	
Dysphagia subjects affected / exposed occurrences (all)	12 / 313 (3.83%) 12	19 / 313 (6.07%) 19	
Gastrooesophageal Reflux Disease			

subjects affected / exposed occurrences (all)	10 / 313 (3.19%) 10	18 / 313 (5.75%) 18	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	184 / 313 (58.79%)	193 / 313 (61.66%)	
occurrences (all)	184	195	
Dry Skin			
subjects affected / exposed	58 / 313 (18.53%)	63 / 313 (20.13%)	
occurrences (all)	59	63	
Dermatitis Acneiform			
subjects affected / exposed	42 / 313 (13.42%)	58 / 313 (18.53%)	
occurrences (all)	42	58	
Pruritus			
subjects affected / exposed	40 / 313 (12.78%)	47 / 313 (15.02%)	
occurrences (all)	40	48	
Alopecia			
subjects affected / exposed	16 / 313 (5.11%)	18 / 313 (5.75%)	
occurrences (all)	16	18	
Erythema			
subjects affected / exposed	11 / 313 (3.51%)	16 / 313 (5.11%)	
occurrences (all)	11	16	
Skin Exfoliation			
subjects affected / exposed	16 / 313 (5.11%)	8 / 313 (2.56%)	
occurrences (all)	16	8	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	6 / 313 (1.92%)	16 / 313 (5.11%)	
occurrences (all)	6	16	
Proteinuria			
subjects affected / exposed	8 / 313 (2.56%)	18 / 313 (5.75%)	
occurrences (all)	8	18	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	41 / 313 (13.10%)	46 / 313 (14.70%)	
occurrences (all)	44	47	
Arthralgia			

subjects affected / exposed	27 / 313 (8.63%)	37 / 313 (11.82%)	
occurrences (all)	28	38	
Musculoskeletal Pain			
subjects affected / exposed	23 / 313 (7.35%)	34 / 313 (10.86%)	
occurrences (all)	24	34	
Pain in Extremity			
subjects affected / exposed	20 / 313 (6.39%)	24 / 313 (7.67%)	
occurrences (all)	22	24	
Musculoskeletal Chest Pain			
subjects affected / exposed	15 / 313 (4.79%)	19 / 313 (6.07%)	
occurrences (all)	15	20	
Muscle Spasms			
subjects affected / exposed	17 / 313 (5.43%)	16 / 313 (5.11%)	
occurrences (all)	17	16	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	26 / 313 (8.31%)	33 / 313 (10.54%)	
occurrences (all)	28	36	
Upper Respiratory Tract Infection			
subjects affected / exposed	30 / 313 (9.58%)	30 / 313 (9.58%)	
occurrences (all)	30	30	
Pneumonia			
subjects affected / exposed	16 / 313 (5.11%)	9 / 313 (2.88%)	
occurrences (all)	24	23	
Bronchitis			
subjects affected / exposed	18 / 313 (5.75%)	10 / 313 (3.19%)	
occurrences (all)	19	12	
Sinusitis			
subjects affected / exposed	8 / 313 (2.56%)	16 / 313 (5.11%)	
occurrences (all)	8	16	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	24 / 313 (7.67%)	35 / 313 (11.18%)	
occurrences (all)	27	40	
Anorexia			

subjects affected / exposed	75 / 313 (23.96%)	104 / 313 (33.23%)	
occurrences (all)	76	105	
Decreased Appetite			
subjects affected / exposed	21 / 313 (6.71%)	36 / 313 (11.50%)	
occurrences (all)	21	36	
Hypokalaemia			
subjects affected / exposed	21 / 313 (6.71%)	17 / 313 (5.43%)	
occurrences (all)	21	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2005	Inclusion and exclusion criteria were revised; secondary outcome measures were revised; pharmacokinetic outcome measures for bevacizumab were revised; dosing information for both Tarceva and bevacizumab were revised; the frequency of survival follow-up increased to every 6 weeks; number of study centers increased; medical monitor changed; informed consent form was revised.
31 October 2005	Participants with squamous cell carcinoma and participants with treated brain metastases were included; eligibility criteria was revised; secondary objective regarding the association of survival, progression-free survival, and treatment effect with markers of epidermal growth factor receptor (EGFR) expression has been modified to include EGFR gene copy number measured by fluorescence in situ hybridization (FISH); exclusion criteria was changed to allow non-small cell lung cancer (NSCLC) participants with certain profiles to enroll; the aspirin requirement was revised to a daily dose not exceeding 325 miligrams (mg); the approach for statistical testing of the primary and secondary endpoints was clarified.
03 March 2006	The medical monitor and alternate contact changed; eligibility criteria was revised; secondary objective regarding the association of survival, progression-free survival, and treatment effect with markers of epidermal growth factor receptor (EGFR) expression has been modified to include EGFR gene copy number measured by fluorescence in situ hybridization (FISH); exclusion criteria was changed to allow non-small cell lung cancer (NSCLC) participants with certain profiles to enroll; dose modification was revised to state that if Tarceva is permanently discontinued; the participant should be discontinued from the treatment phase of the study and should enter survival follow-up; the aspirin requirement was revised to a daily dose not exceeding 325 miligrams (mg); antiplatelet drugs given at standard doses were permitted; the approach for statistical testing of the primary and secondary endpoints was clarified; safety monitoring plan was described.
30 November 2006	Revisions to the statistical methods introducing interim efficacy analysis; updated background information on bevacizumab and erlotinib was provided; dose modification criteria was modified; information was updated for the guidelines on the management of certain study treatment-related toxicities.
12 March 2009	AE data collection was limited to collection of SAEs for the remainder of the study.
11 October 2012	No further patient data was to be collected except for SAEs reporting via MedWatch FDA 3500 forms and no AEs were collected in the clinical database any longer; Participants began receiving study drugs directly from Astellas Pharma US, Inc. labeled as "erlotinib" at their current dosage; no dose adjustments were permitted

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

