



Clinical trial results:

A Phase III, Randomized, Double-blinded, Parallel Group, Multi-centre Study to Assess the Efficacy and Safety of ZD6474 (ZACTIMA™) in Combination with Pemetrexed (Alimta®) versus Pemetrexed alone in Patients with Locally-Advanced or Metastatic (stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-cancer Therapy Summary

EudraCT number	2006-003695-35
Trial protocol	SE DE GR PT IT BE GB ES FR
Global end of trial date	14 February 2023

Results information

Result version number	v1 (current)
This version publication date	18 January 2025
First version publication date	18 January 2025

Trial information

Trial identification

Sponsor protocol code	D4200C00036
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00418886
WHO universal trial number (UTN)	-
Other trial identifiers	Sanofi: LPS15296

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	50 Binney Street, Cambridge, Massachusetts, United States, 02142
Public contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.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	05 September 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 February 2023
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 demonstrate an improvement in progression-free survival (PFS) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, for the combination of vandetanib plus pemetrexed compared with pemetrexed plus placebo in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of first line anti-cancer therapy (not including an adjuvant regimen).

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 January 2007
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	Argentina: 20
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Colombia: 10
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Israel: 61
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Philippines: 28
Country: Number of subjects enrolled	Portugal: 9

Country: Number of subjects enrolled	South Africa: 36
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 10
Worldwide total number of subjects	534
EEA total number of subjects	184

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)	370
From 65 to 84 years	164
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a parallel-group, placebo-controlled study. First participant enrolled 09 January 2007, last participant enrolled 29 February 2008, cut off date 05 September 2008.

Pre-assignment

Screening details:

A total of 534 participants were randomized in the study. Of which, 124 participants from vandetanib group and 110 participants from placebo group completed or discontinued treatment in randomized period entered survival follow-up period. All participants entered survival follow-up period completed end of treatment or died due to any cause.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Vandetanib Plus Pemetrexed

Arm description:

Vandetanib [100 milligram (mg) daily] plus pemetrexed [500 mg/metre square (m^2) given on Day 1 of each 21-day cycle].

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	
Other name	ZD6474, ZACTIMA™
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Vandetanib 100 mg oral tablet administered daily in each 21-day cycle.

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

Dosage and administration details:

Pemetrexed 500 mg/ m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Arm title	Placebo Plus Pemetrexed
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Arm description:

Placebo plus pemetrexed (500 mg/ m^2 given on Day 1 of each 21-day cycle).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo oral tablet administered daily in each 21-day cycle.

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

Dosage and administration details:

Pemetrexed 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Number of subjects in period 1	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed
Started	256	278
Completed	30	23
Not completed	226	255
Consent withdrawn by subject	9	10
Death	122	147
Randomised but no treatment received	-	1
Withdrawn due to other reason	1	-
Discontinue treatment survival follow-up	90	91
Lost to follow-up	4	6

Baseline characteristics

Reporting groups

Reporting group title	Vandetanib Plus Pemetrexed
Reporting group description: Vandetanib [100 milligram (mg) daily] plus pemetrexed [500 mg/metre square (m ²) given on Day 1 of each 21-day cycle].	
Reporting group title	Placebo Plus Pemetrexed
Reporting group description: Placebo plus pemetrexed (500 mg/m ² given on Day 1 of each 21-day cycle).	

Reporting group values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed	Total
Number of subjects	256	278	534
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	58.7 ± 9.95	60.2 ± 9.5	-
Gender categorical Units: Subjects			
Female	97	107	204
Male	159	171	330

End points

End points reporting groups

Reporting group title	Vandetanib Plus Pemetrexed
Reporting group description: Vandetanib [100 milligram (mg) daily] plus pemetrexed [500 mg/metre square (m ²) given on Day 1 of each 21-day cycle].	
Reporting group title	Placebo Plus Pemetrexed
Reporting group description: Placebo plus pemetrexed (500 mg/m ² given on Day 1 of each 21-day cycle).	

Primary: Progression-Free Survival in the Overall Population

End point title	Progression-Free Survival in the Overall Population ^[1]
End point description: Median time (in weeks) from randomization until objective disease progression or death (by any cause in the absence of objective progression) provided death is within 3 months from the last evaluable RECIST assessment. The full analysis set included all randomized participants.	
End point type	Primary
End point timeframe: RECIST tumour assessments carried out every 6 weeks (+/- 3 days) from randomization until objective progression.	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.	

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: weeks				
median (confidence interval 95%)	17.6 (13.4 to 18.9)	11.9 (11.4 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival in the Female Population

End point title	Progression-Free Survival in the Female Population ^[2]
End point description: Median time (in weeks) from randomization until objective disease progression or death (by any cause in the absence of objective progression) provided death is within 3 months from the last evaluable RECIST assessment. The female analysis set included all randomized female participants.	
End point type	Primary
End point timeframe: RECIST tumour assessments carried out every 6 weeks (+/- 3 days) from randomization until objective progression.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	107		
Units: weeks				
median (confidence interval 95%)	17.9 (14.7 to 22.7)	13.0 (11.1 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
The OS is defined as the time from date of randomization until death. Any participant not known to have died at the time of analysis was censored based on the last recorded date on which the participant was known to be alive (i.e, their status must be known at the censored date and should not be lost to follow up or unknown). The full analysis set included all randomized participants.	
End point type	Secondary
End point timeframe:	
Time to death in months	

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: months				
median (confidence interval 95%)	10.5 (8.9 to 12.3)	9.2 (7.1 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	
The ORR is the number of participants that are responders i.e, those participants with a confirmed best objective response of complete response (CR) or partial response (PR) as defined by RECIST criteria.	

The categories for best objective response are CR, PR, stable disease (SD) $\geq$ 6 weeks, progressive disease (PD) or NE. The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

Each participant was assessed for objective response from the sequence of RECIST scan data up to data cut off. RECIST tumour assessments carried out every 6 weeks (+/- 3 days) from randomization until objective progression

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: percentage of participants				
number (not applicable)	19.1	7.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

The DCR is defined as the number of patients who achieved disease control at 6 weeks following randomization. Disease control at 6 weeks is defined as a best objective response of complete response (CR), partial response (PR) or stable disease (SD) $\geq$ 6 weeks. The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

RECIST tumour assessments carried out every 6 weeks (+/- 3 days) from randomization until objective progression

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: percentage of participants				
number (not applicable)	56.6	45.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
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End point description:

Response is defined as a confirmed best objective response of CR or PR. Duration of response is defined as time from the date of first documented response until date of documented progression or death in the absence of disease progression (provided death is within 3 months of last RECIST assessment). The full analysis set included all randomized participants. Only participants with response are analyzed for this outcome measure.

End point type	Secondary
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End point timeframe:

RECIST tumour assessments carried out every 6 weeks (+/- 3 days) from randomization until objective progression

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	22		
Units: weeks				
median (confidence interval 95%)	24.1 (17.4 to 30.0)	24.4 (18.0 to 32.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Disease-related Symptoms (TDS) by Lung Cancer Symptom Scale (LCSS) Total Score

End point title	Time to Deterioration of Disease-related Symptoms (TDS) by Lung Cancer Symptom Scale (LCSS) Total Score
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End point description:

TDS is the interval from the date of randomization to the first assessment of worsened without an improvement in the next 21 days. A deterioration in symptoms is defined as a single visit assessment of 'worsened' with no visit assessment of 'improved' within the next 21 days. The LCSS scale measures changes in symptoms associated with lung cancer. The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

LCSS questionnaires are to be administered every 3 weeks after randomization

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: weeks				
median (confidence interval 95%)	18.1 (15.1 to 23.6)	12.1 (9.7 to 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Disease-related Symptoms by Average Symptom Burden Index (ASBI) Score

End point title	Time to Deterioration of Disease-related Symptoms by Average Symptom Burden Index (ASBI) Score
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End point description:

Time to deterioration is defined as the interval from the date of randomization to the first assessment of worsened without an improvement in the next 21 days. A deterioration in symptoms is defined as a single visit assessment of 'worsened' with no visit assessment of 'improved' within the next 21 days. The ASBI is derived from 6 of LCSS's 9 items. The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

ASBI is a score taken from the LCSS questionnaires which are to be administered every 3 weeks after randomization

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: weeks				
median (confidence interval 95%)	16.0 (14.0 to 20.3)	13.4 (10.3 to 17.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Longitudinal Analysis of Lung Cancer Symptom Scale Total Score

End point title	Longitudinal Analysis of Lung Cancer Symptom Scale Total Score
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End point description:

The longitudinal data analysis will include all non-missing visit scores and the model will include only the first 12 weeks of data. LCSS total score is an average of all 9 visual analogue participant scales from "none" [0 millimeter (mm)] to "as much as it could be" (100 mm). The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

LCSS questionnaires are to be administered every 3 weeks after randomization

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: mms on a visual analogue scale				
least squares mean (standard error)	25.7 ($\pm$ 2.85)	28.3 ($\pm$ 2.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Longitudinal Analysis of Average Symptom Burden Index Score

End point title	Longitudinal Analysis of Average Symptom Burden Index Score
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End point description:

The longitudinal data analysis will include all non-missing visit scores and the model will include only the first 12 weeks of data. ASBI is an average of the 6 symptom visual analogue patient scales from "none" (0 mm) to "as much as it could be" (100 mm). The full analysis set included all randomized participants.

End point type	Secondary
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End point timeframe:

ASBI is a score taken from the LCSS questionnaires administered every 3 weeks after randomization

End point values	Vandetanib Plus Pemetrexed	Placebo Plus Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	278		
Units: mms on a visual analogue scale				
least squares mean (standard error)	21.7 ($\pm$ 2.75)	24.3 ($\pm$ 2.67)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent up to the study completion for each participant, approximately 193 months.

Adverse event reporting additional description:

Analysis was performed on safety analysis set. 4 participants randomized to "Placebo Plus Pemetrexed" reporting group were erroneously assigned to receive vandetanib during Randomized Period. Therefore, total number of participants received "Vandetanib Plus pemetrexed" was 260 and "Placebo Plus Pemetrexed" was 273 during Randomized Period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0-25.1
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Reporting groups

Reporting group title	Randomized Period: Vandetanib Plus Pemetrexed
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Reporting group description:

Vandetanib (100 mg daily) plus pemetrexed (500 mg/m² given on Day 1 of each 21-day cycle) in randomized period.

Reporting group title	Randomized Period: Placebo Plus Pemetrexed
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Reporting group description:

Placebo plus pemetrexed (500 mg/m² given on Day 1 of each 21-day cycle) in randomized period.

Reporting group title	Survival Follow-up Period: Vandetanib Plus Pemetrexed
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Reporting group description:

Vandetanib (100 mg daily) plus pemetrexed (500 mg/m² given on Day 1 of each 21-day cycle) in survival follow-up period.

Reporting group title	Survival Follow-up Period: Placebo Plus Pemetrexed
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Reporting group description:

Placebo plus pemetrexed (500 mg/m² given on Day 1 of each 21-day cycle) in survival follow-up period.

Serious adverse events	Randomized Period: Vandetanib Plus Pemetrexed	Randomized Period: Placebo Plus Pemetrexed	Survival Follow-up Period: Vandetanib Plus Pemetrexed
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 260 (32.31%)	94 / 273 (34.43%)	7 / 124 (5.65%)
number of deaths (all causes)	122	147	63
number of deaths resulting from adverse events	2	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic Pain			

subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	2 / 260 (0.77%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena Cava Thrombosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 260 (2.69%)	3 / 273 (1.10%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 9	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance Status Decreased			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organ Failure			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

General Physical Health Deterioration			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait Disturbance			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 260 (0.38%)	6 / 273 (2.20%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease Progression			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Atelectasis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis Allergic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	3 / 260 (1.15%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary Oedema			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary Fistula			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	3 / 260 (1.15%)	6 / 273 (2.20%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	1 / 3	4 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 260 (0.38%)	3 / 273 (1.10%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic Pain			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	3 / 260 (1.15%)	4 / 273 (1.47%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 260 (0.77%)	3 / 273 (1.10%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 5	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 2	0 / 0
Dyspnoea			
subjects affected / exposed	8 / 260 (3.08%)	10 / 273 (3.66%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 10	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cough			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			

subjects affected / exposed	1 / 260 (0.38%)	2 / 273 (0.73%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Body Temperature Increased			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International Normalised Ratio Increased			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaesthetic Complication Cardiac			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haemorrhage			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 260 (0.77%)	4 / 273 (1.47%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Incompetence			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	0 / 260 (0.00%)	0 / 273 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tachycardia			
subjects affected / exposed	2 / 260 (0.77%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			

subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	2 / 260 (0.77%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac Failure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Artery Embolism			
subjects affected / exposed	0 / 260 (0.00%)	0 / 273 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			

subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphasia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	3 / 260 (1.15%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 260 (0.77%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			

subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 260 (0.77%)	7 / 273 (2.56%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 260 (1.15%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 260 (0.77%)	5 / 273 (1.83%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	3 / 260 (1.15%)	4 / 273 (1.47%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal Detachment			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Visual Impairment			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 260 (0.77%)	4 / 273 (1.47%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	2 / 260 (0.77%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Perforation			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Ulcer Haemorrhage			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer			

subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 260 (0.77%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reflux Oesophagitis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 260 (1.15%)	6 / 273 (2.20%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 4	2 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photosensitivity Reaction			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 260 (0.77%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Prerenal Failure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal Colic			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 260 (1.15%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular Weakness			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 260 (0.38%)	3 / 273 (1.10%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pathological Fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck Pain			
subjects affected / exposed	2 / 260 (0.77%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	2 / 260 (0.77%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 260 (0.00%)	0 / 273 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter Related Infection			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			

subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 260 (0.38%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	1 / 260 (0.38%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 260 (2.69%)	10 / 273 (3.66%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	1 / 7	1 / 13	0 / 1
deaths causally related to treatment / all	1 / 3	0 / 2	0 / 0
Lung Infection			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	4 / 260 (1.54%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lobar Pneumonia			

subjects affected / exposed	1 / 260 (0.38%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 260 (0.00%)	0 / 273 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 260 (0.00%)	2 / 273 (0.73%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 260 (0.00%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 260 (0.77%)	0 / 273 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 273 (0.37%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Survival Follow-up		
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	Period: Placebo Plus Pemetrexed		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 110 (2.73%)		
number of deaths (all causes)	58		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vena Cava Thrombosis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Performance Status Decreased				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Organ Failure				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General Physical Health Deterioration				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait Disturbance				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease Progression				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alveolitis Allergic			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Distress			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pulmonary Oedema				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Fistula				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleuritic Pain				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial Lung Disease				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Body Temperature Increased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil Count Decreased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
International Normalised Ratio Increased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anaesthetic Complication Cardiac			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus Fracture			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head Injury			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural Haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic Valve Incompetence			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina Pectoris			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial Flutter			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus Tachycardia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial Effusion			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral Artery Embolism			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral Ischaemia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Monoparesis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphasia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular Accident			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal Detachment			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Visual Impairment			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lower Gastrointestinal Haemorrhage				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large Intestine Perforation				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal Obstruction				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Ulcer Haemorrhage				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric Ulcer				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Lower				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reflux Oesophagitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Pemphigoid			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Photosensitivity Reaction			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Prerenal Failure			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Colic			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Impairment			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pathological Fracture			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter Related Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobar Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Randomized Period: Vandetanib Plus Pemetrexed	Randomized Period: Placebo Plus Pemetrexed	Survival Follow-up Period: Vandetanib Plus Pemetrexed
Total subjects affected by non-serious adverse events			
subjects affected / exposed	234 / 260 (90.00%)	242 / 273 (88.64%)	22 / 124 (17.74%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	14 / 260 (5.38%)	21 / 273 (7.69%)	0 / 124 (0.00%)
occurrences (all)	18	24	0
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 260 (11.15%)	8 / 273 (2.93%)	2 / 124 (1.61%)
occurrences (all)	35	9	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 260 (11.15%)	43 / 273 (15.75%)	4 / 124 (3.23%)
occurrences (all)	34	63	4
Fatigue			

subjects affected / exposed occurrences (all)	99 / 260 (38.08%) 127	118 / 273 (43.22%) 159	2 / 124 (1.61%) 2
Oedema Peripheral subjects affected / exposed occurrences (all)	11 / 260 (4.23%) 12	22 / 273 (8.06%) 24	1 / 124 (0.81%) 1
Pyrexia subjects affected / exposed occurrences (all)	25 / 260 (9.62%) 32	43 / 273 (15.75%) 60	2 / 124 (1.61%) 2
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	18 / 260 (6.92%) 18	6 / 273 (2.20%) 6	0 / 124 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	66 / 260 (25.38%) 75	59 / 273 (21.61%) 68	4 / 124 (3.23%) 4
Dyspnoea subjects affected / exposed occurrences (all)	49 / 260 (18.85%) 53	56 / 273 (20.51%) 60	2 / 124 (1.61%) 2
Epistaxis subjects affected / exposed occurrences (all)	17 / 260 (6.54%) 22	12 / 273 (4.40%) 15	1 / 124 (0.81%) 2
Haemoptysis subjects affected / exposed occurrences (all)	12 / 260 (4.62%) 14	17 / 273 (6.23%) 21	1 / 124 (0.81%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	11 / 260 (4.23%) 12	16 / 273 (5.86%) 16	0 / 124 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	14 / 260 (5.38%) 14	17 / 273 (6.23%) 17	0 / 124 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	34 / 260 (13.08%) 38	27 / 273 (9.89%) 27	0 / 124 (0.00%) 0
Investigations			

Weight Decreased subjects affected / exposed occurrences (all)	23 / 260 (8.85%) 23	15 / 273 (5.49%) 15	0 / 124 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	20 / 260 (7.69%) 26	23 / 273 (8.42%) 30	0 / 124 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	28 / 260 (10.77%) 35	40 / 273 (14.65%) 50	1 / 124 (0.81%) 1
Blood and lymphatic system disorders			
Leukopenia subjects affected / exposed occurrences (all)	18 / 260 (6.92%) 27	17 / 273 (6.23%) 22	0 / 124 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	21 / 260 (8.08%) 32	26 / 273 (9.52%) 35	0 / 124 (0.00%) 0
Anaemia subjects affected / exposed occurrences (all)	19 / 260 (7.31%) 27	54 / 273 (19.78%) 59	0 / 124 (0.00%) 0
Eye disorders			
Lacrimation Increased subjects affected / exposed occurrences (all)	12 / 260 (4.62%) 12	14 / 273 (5.13%) 16	0 / 124 (0.00%) 0
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	16 / 260 (6.15%) 21	15 / 273 (5.49%) 17	1 / 124 (0.81%) 1
Abdominal Pain Upper subjects affected / exposed occurrences (all)	14 / 260 (5.38%) 16	17 / 273 (6.23%) 18	0 / 124 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	52 / 260 (20.00%) 69	53 / 273 (19.41%) 65	3 / 124 (2.42%) 3
Diarrhoea subjects affected / exposed occurrences (all)	66 / 260 (25.38%) 95	48 / 273 (17.58%) 66	3 / 124 (2.42%) 3

Dyspepsia subjects affected / exposed occurrences (all)	21 / 260 (8.08%) 25	11 / 273 (4.03%) 11	1 / 124 (0.81%) 1
Nausea subjects affected / exposed occurrences (all)	73 / 260 (28.08%) 100	98 / 273 (35.90%) 167	0 / 124 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	19 / 260 (7.31%) 25	18 / 273 (6.59%) 24	0 / 124 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	37 / 260 (14.23%) 42	55 / 273 (20.15%) 97	3 / 124 (2.42%) 3
Skin and subcutaneous tissue disorders			
Dry Skin subjects affected / exposed occurrences (all)	14 / 260 (5.38%) 14	8 / 273 (2.93%) 9	2 / 124 (1.61%) 2
Acne subjects affected / exposed occurrences (all)	14 / 260 (5.38%) 15	8 / 273 (2.93%) 8	1 / 124 (0.81%) 1
Rash subjects affected / exposed occurrences (all)	99 / 260 (38.08%) 143	71 / 273 (26.01%) 93	3 / 124 (2.42%) 5
Pruritus subjects affected / exposed occurrences (all)	28 / 260 (10.77%) 37	40 / 273 (14.65%) 47	0 / 124 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	14 / 260 (5.38%) 18	12 / 273 (4.40%) 16	1 / 124 (0.81%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	9 / 260 (3.46%) 10	16 / 273 (5.86%) 17	2 / 124 (1.61%) 2
Back Pain subjects affected / exposed occurrences (all)	24 / 260 (9.23%) 25	31 / 273 (11.36%) 32	1 / 124 (0.81%) 1
Musculoskeletal Chest Pain			

subjects affected / exposed occurrences (all)	18 / 260 (6.92%) 21	21 / 273 (7.69%) 26	2 / 124 (1.61%) 2
Musculoskeletal Pain subjects affected / exposed occurrences (all)	11 / 260 (4.23%) 12	23 / 273 (8.42%) 25	1 / 124 (0.81%) 1
Pain In Extremity subjects affected / exposed occurrences (all)	13 / 260 (5.00%) 13	18 / 273 (6.59%) 18	0 / 124 (0.00%) 0
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	12 / 260 (4.62%) 14	14 / 273 (5.13%) 19	0 / 124 (0.00%) 0
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	56 / 260 (21.54%) 72	65 / 273 (23.81%) 82	3 / 124 (2.42%) 3

Non-serious adverse events	Survival Follow-up Period: Placebo Plus Pemetrexed		
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 110 (17.27%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Cancer Pain subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema Peripheral	2 / 110 (1.82%) 2 2 / 110 (1.82%) 2		

subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Investigations			
Weight Decreased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 5		
Headache subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 4		
Blood and lymphatic system disorders			
Leukopenia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Anaemia subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Eye disorders			
Lacrimation Increased subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 3		
Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Nausea			

subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	12		
Stomatitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Acne			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	3		
Back Pain			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Musculoskeletal Chest Pain			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	4		
Musculoskeletal Pain			

subjects affected / exposed occurrences (all) Pain In Extremity subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1 4 / 110 (3.64%) 4		
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2007	• Phase II data suggested a more pronounced benefit for vandetanib in combination with chemotherapy compared with chemotherapy alone in female participants. • To allow participants receiving medications listed in Appendix D, that could not be discontinued, to continue those medications with additional safety precautions. • The per-protocol analysis was to exclude significant protocol deviators.
13 April 2007	• Sample size adjusted to allow for a single interim analysis to assess superiority of PFS and OS. • Renal impairment study showed no significant change in exposure for participants with mild or moderate renal impairment; creatinine clearance < 50 milliliter per minute excluded because of concomitant pemetrexed.
17 December 2008	• Participants continued to follow for survival due to a regulatory request to review further survival information. A further PFS analysis was not anticipated, however maintaining the RECIST schedule for ongoing participants was important to ensure no differential management of participants in terms of duration of treatment as this had a potential to impact the subsequent overall survival analysis. • In addition any participants still receiving vandetanib/placebo should continue to have all safety assessment performed as they were still receiving an investigational product. • No further quality of life or biomarker analyses was performed so it was not necessary for participants to continue to have these assessments. • Following the primary analysis, an additional survival analysis was performed as a consequence of regulatory agency request to provide further mature survival data during their review process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported