



Clinical trial results:

A Single-Arm, Phase 2 Trial of Pemetrexed, Cisplatin, and Bevacizumab as Induction, Followed by Pemetrexed and Bevacizumab as Maintenance, in First-Line Treatment of Nonsquamous Advanced NSCLC

Summary

EudraCT number	2008-006732-35
Trial protocol	DE IT DK ES SE
Global end of trial date	06 December 2013

Results information

Result version number	v1 (current)
This version publication date	04 July 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	H3E-EW-S125
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01004250
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 13034, Trial Alias: H3E-EW-S125

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Participants with advanced non-small cell lung cancer (NSCLC) will receive a first-line treatment of Pemetrexed, Cisplatin and Bevacizumab as induction therapy followed by a maintenance treatment of Pemetrexed and Bevacizumab. Treatment will continue until disease progression or unacceptable toxicity occurs. The primary objective of this study is to measure how long this treatment could prevent the disease progression.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Sweden: 18
Worldwide total number of subjects	109
EEA total number of subjects	109

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)	75
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study had 3 periods: a baseline period; a study treatment period, including both induction (Ind) and maintenance (Maint) treatment; and a follow-up period.

Period 1

Period 1 title	Induction Therapy Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Study Treatment Induction
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Arm description:

Induction Therapy:

Bevacizumab: 7.5 milligram per kilogram (mg/kg) given intravenously on Day 1 for four cycles (cycle=21 days) of Induction Therapy.

Pemetrexed: 500 milligram per square meter (mg/m²) given intravenously on Day 1 for four cycles of Induction Therapy.

Cisplatin: 75 mg/m² given intravenously on Day 1 for a maximum of 4 cycles.

Maintenance Therapy:

Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.

Pemetrexed: 500 mg/m² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.

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

Dosage and administration details:

7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.

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

Dosage and administration details:

Cisplatin: 75 mg/m² given intravenously on Day 1 for a maximum of 4 cycles.

Number of subjects in period 1	Study Treatment Induction
Started	109
Death (any cause) or Disease Progression	21 ^[1]
Received at Least One Dose of Study Drug	109
Completed	94
Not completed	15
Physician decision	2
Adverse event, non-fatal	10
Withdrawal by Subject	2
Entry Criteria Not Met	1

Notes:

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

Justification: Participants who died or had disease progression are considered to have completed the phase. Of the 109 participants who started the Induction Therapy Period, 15 did not complete this phase.

Period 2

Period 2 title	Maintenance Therapy Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Study Treatment Maintenance
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Arm description:

Maintenance Therapy:

Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.

Pemetrexed: 500 mg/m² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed: 500 mg/m² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use
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Dosage and administration details:

Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.

Number of subjects in period 2^[2]	Study Treatment Maintenance
Started	72
Did not enter Maintenance Therapy Period	22 ^[3]
Completed	46
Not completed	26
Physician decision	4
Adverse event, non-fatal	15
Withdrawal by Subject	5
Protocol Violation	1
Lost to follow-up	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who died or had disease progression are considered to have completed the phase. Participants who did not enter the Maintenance Therapy Period included: 21 participants who died (any cause) or had disease progression during the Induction Therapy Period, and 1 participant who had a performance status of 2.

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

Justification: Eight participants did not enter the Follow-Up Period: 4 participants died during the Induction Therapy Period and 1 died during the Maintenance Therapy Period; 2 participants withdrew (1 Induction, 1 Maintenance), 1 participant was lost to follow-up in the Maintenance Therapy Period.

Baseline characteristics

Reporting groups

Reporting group title	Study Treatment Induction
Reporting group description:	
Induction Therapy:	
Bevacizumab: 7.5 milligram per kilogram (mg/kg) given intravenously on Day 1 for four cycles (cycle=21 days) of Induction Therapy.	
Pemetrexed: 500 milligram per square meter (mg/m ²) given intravenously on Day 1 for four cycles of Induction Therapy.	
Cisplatin: 75 mg/m ² given intravenously on Day 1 for a maximum of 4 cycles.	
Maintenance Therapy:	
Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.	
Pemetrexed: 500 mg/m ² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.	

Reporting group values	Study Treatment Induction	Total	
Number of subjects	109	109	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	75	75	
From 65-84 years	34	34	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	59.1		
standard deviation	± 8.8	-	
Gender, Male/Female			
Units: participants			
Female	45	45	
Male	64	64	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	108	108	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment			

Units: Subjects			
Spain	12	12	
Denmark	19	19	
Germany	25	25	
Italy	35	35	
Sweden	18	18	
ECOG Performance Status			
<p>Eastern Cooperative Oncology Group (ECOG) Performance Status Classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death):</p> <p>0 - Fully Active</p> <p>1 - Ambulatory, Restricted Strenuous Activity</p> <p>2 - Ambulatory, No Work Activities</p> <p>3 - Partially Confined to Bed, Limited Self Care</p> <p>4 - Completely Disabled</p> <p>5 - Death</p>			
Units: Subjects			
ECOG 0	59	59	
ECOG 1	50	50	
Initial Pathological Diagnosis			
Non-Small Cell Lung Cancer (NSCLC)			
Units: Subjects			
Adenocarcinoma	99	99	
Large Cell Lung Carcinoma	3	3	
Poorly Differentiated NSCLC	3	3	
Other	4	4	
Stage of Disease			
<p>According to American Joint Committee on Cancer (AJCC) Cancer Staging Manual, sixth edition (2002), stage of disease means how big the tumor is and how far it has spread. Stages range from 0 (not spread) to IV (spread throughout the body).</p> <p>Stage IIIB - the cancer has spread to nearby tissue or spread to far away lymph nodes but not spread to other organs</p> <p>Stage IV - the cancer has spread to other organs of the body such as the other lung, brain, or liver</p>			
Units: Subjects			
Stage IIIB	10	10	
Stage IV	99	99	
Tobacco Use			
Units: Subjects			
Never Smoked	15	15	
Ex-Smoker	66	66	
Current Smoker	28	28	

End points

End points reporting groups

Reporting group title	Study Treatment Induction
Reporting group description:	
Induction Therapy:	
Bevacizumab: 7.5 milligram per kilogram (mg/kg) given intravenously on Day 1 for four cycles (cycle=21 days) of Induction Therapy.	
Pemetrexed: 500 milligram per square meter (mg/m ²) given intravenously on Day 1 for four cycles of Induction Therapy.	
Cisplatin: 75 mg/m ² given intravenously on Day 1 for a maximum of 4 cycles.	
Maintenance Therapy:	
Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.	
Pemetrexed: 500 mg/m ² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.	
Reporting group title	Study Treatment Maintenance
Reporting group description:	
Maintenance Therapy:	
Bevacizumab: 7.5 mg/kg given intravenously on Day 1 of each cycle (cycle=21 days) and continued until progression or unacceptable toxicity.	
Pemetrexed: 500 mg/m ² given intravenously on Day 1 of each cycle and continued until progression or unacceptable toxicity.	

Primary: Progression-Free Survival

End point title	Progression-Free Survival ^[1]
End point description:	
Progression-Free Survival (PFS) is defined as the time from the date of study enrollment to the first date of objectively determined PD or death from any cause. PD is defined using Response Evaluation Criteria in Solid Tumours (RECIST) Guidelines (Version 1.0), as at least a 20% increase in the sum of longest diameter (LD) of target lesions, taking as references the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. For participants not known to have died as of the data cut-off date and who do not have objective PD, PFS will be censored at the date of the last objective progression-free disease assessment. For participants who receive subsequent systemic anticancer therapy, PFS will be censored at the date of the last objective progression-free disease assessment prior to post-discontinuation systemic therapy.	
End point type	Primary
End point timeframe:	
From enrollment to the first date of objectively determined Progressive Disease (PD) or death from any cause (every other cycle during study treatment and then every 6 weeks during follow-up period)(Baseline up to 36.1 Months)	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Descriptive statistics are used to represent objective PFS from the date of study enrollment to time of event of PD or death and reported as median months with 90% confidence interval.	

End point values	Study Treatment Induction			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Months				
median (confidence interval 90%)	6.9 (5.7 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall Survival (OS) is defined as the time from the date of study enrollment to the date of death from any cause. For participants not known to have died as of the data cut-off date, OS will be censored at the last contact date.

End point type	Secondary
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End point timeframe:

From enrollment to the date of death from any cause (every cycle during study treatment, every 6 weeks during follow-up period until PD, and then at least every 3 Months) (Baseline up to 36.3 Months)

End point values	Study Treatment Induction			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Months				
median (confidence interval 95%)	14.7 (11.5 to 19.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with confirmed complete response or partial response during study treatment (Induction and Maintenance)

End point title	Percentage of participants with confirmed complete response or partial response during study treatment (Induction and Maintenance)
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End point description:

Overall Response Rate (ORR) is defined as the percentage of participants whose best response is complete response (CR) or partial response (PR) per RECIST Guidelines, Version 1.0. CR is disappearance of all tumor lesions. PR is either a) at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LDs, or b) complete disappearance of target lesions, with persistence (but not worsening) of 1 or more nontarget lesions. In either case, no new lesions may have appeared.

End point type	Secondary
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End point timeframe:

From enrollment to objectively determined PD (assessment during study treatment completed at every other cycle till PD and at 30 day follow-up)(Baseline up to 104.1 Weeks)

End point values	Study Treatment Induction			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Percentage of Participants				
number (confidence interval 95%)	42.2 (32.8 to 52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with confirmed response complete or partial response during the Induction treatment only

End point title	Percentage of participants with confirmed response complete or partial response during the Induction treatment only
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End point description:

CR and PR defined per RECIST Guidelines, Version 1.0. CR is disappearance of all tumor lesions. PR is either a) at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LDs, or b) complete disappearance of target lesions, with persistence (but not worsening) of 1 or more nontarget lesions. In either case, no new lesions may have appeared.

End point type	Secondary
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End point timeframe:

From the time of study enrollment to the first date of objectively determined PD during the induction therapy (assessment during study treatment completed at every other cycle up to four cycles) (Baseline up to 4 cycles)

End point values	Study Treatment Induction			
Subject group type	Reporting group			
Number of subjects analysed	109			
Units: Percentage of Participants				
number (confidence interval 95%)	34.9 (26 to 44.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with confirmed complete response or partial response during the maintenance therapy only

End point title	Percentage of participants with confirmed complete response or
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End point description:

CR and PR defined per RECIST Guidelines, Version 1.0. CR is disappearance of all tumor lesions. PR is either a) at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LDs, or b) complete disappearance of target lesions, with persistence (but not worsening) of 1 or more nontarget lesions. In either case, no new lesions may have appeared.

End point type

Secondary

End point timeframe:

From the start of the maintenance to the first date of objectively determined PD during the maintenance therapy (assessment during maintenance treatment completed at every other cycle till PD and at 30 day follow-up)(Cycle 5 up to 104.1 Weeks)

End point values	Study Treatment Maintenance			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Percentage of Participants				
number (confidence interval 95%)	11.1 (4.9 to 20.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

H3E-EW-S125

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Pemetrexed 500 mg/m2 + Cisplatin 75 mg/m2 + Bevacizumab 7.5 m
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Reporting group description: -

Serious adverse events	Pemetrexed 500 mg/m2 + Cisplatin 75 mg/m2 + Bevacizumab 7.5 m		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 109 (35.78%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastatic pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
tumour pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	3 / 109 (2.75%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
hypotension				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
thrombosis				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
asthenia				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
chest pain				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
general physical health deterioration				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
impaired healing				
alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
oedema peripheral			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
pyrexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
sudden death			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
haemoptysis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
idiopathic pulmonary fibrosis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pleural effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
pneumonia aspiration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
pulmonary embolism			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
respiratory failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
platelet count decreased			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
white blood cell count decreased alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
atrial fibrillation alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
left ventricular dysfunction alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
myocardial infarction alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
pericardial effusion alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
coma alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
syncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
transient global amnesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
transient ischaemic attack			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
febrile neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
leukopenia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
lymphopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
thrombocytopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
constipation			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
diarrhoea				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	3 / 109 (2.75%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
gastrointestinal perforation				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
large intestine perforation				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
nausea				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	4 / 109 (3.67%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	3 / 109 (2.75%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			

Renal and urinary disorders			
renal failure acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
bone pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
bronchopneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
lower respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
postoperative wound infection			

alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
respiratory tract infection				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
upper respiratory tract infection				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
urinary tract infection				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
cachexia				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
decreased appetite				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
dehydration				
alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
hyperkalaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pemetrexed 500 mg/m2 + Cisplatin 75 mg/m2 + Bevacizumab 7.5 m		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 109 (92.66%)		
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	23 / 109 (21.10%)		
occurrences (all)	26		
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	12		
chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	9 / 109 (8.26%)		
occurrences (all)	10		
fatigue			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	51 / 109 (46.79%)		
occurrences (all)	63		
influenza like illness			

<p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 109 (6.42%)</p> <p>7</p>		
<p>mucosal inflammation</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 109 (12.84%)</p> <p>20</p>		
<p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 109 (12.84%)</p> <p>14</p>		
<p>pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 109 (6.42%)</p> <p>7</p>		
<p>pyrexia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 109 (15.60%)</p> <p>34</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dysphonia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dyspnoea</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>epistaxis</p> <p>alternative dictionary used: MedDRA 16.1</p>	<p>22 / 109 (20.18%)</p> <p>29</p> <p>8 / 109 (7.34%)</p> <p>8</p> <p>16 / 109 (14.68%)</p> <p>22</p>		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>rhinorrhoea</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>28 / 109 (25.69%)</p> <p>38</p> <p>8 / 109 (7.34%)</p> <p>9</p> <p>8 / 109 (7.34%)</p> <p>10</p>		
<p>Psychiatric disorders</p> <p>anxiety</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 109 (5.50%)</p> <p>6</p> <p>12 / 109 (11.01%)</p> <p>12</p>		
<p>Investigations</p> <p>blood creatinine increased</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>haemoglobin decreased</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>weight decreased</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 109 (6.42%)</p> <p>7</p> <p>7 / 109 (6.42%)</p> <p>9</p> <p>11 / 109 (10.09%)</p> <p>11</p>		
<p>Nervous system disorders</p> <p>dizziness</p> <p>alternative dictionary used: MedDRA 16.1</p>			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dysgeusia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>headache</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>neuropathy peripheral</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>paraesthesia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>peripheral sensory neuropathy</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 109 (9.17%)</p> <p>11</p> <p>10 / 109 (9.17%)</p> <p>10</p> <p>19 / 109 (17.43%)</p> <p>22</p> <p>6 / 109 (5.50%)</p> <p>9</p> <p>10 / 109 (9.17%)</p> <p>11</p> <p>17 / 109 (15.60%)</p> <p>20</p>		
<p>Blood and lymphatic system disorders</p> <p>anaemia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>leukopenia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>neutropenia</p> <p>alternative dictionary used: MedDRA 16.1</p>	<p>9 / 109 (8.26%)</p> <p>9</p> <p>11 / 109 (10.09%)</p> <p>31</p>		

subjects affected / exposed occurrences (all)	22 / 109 (20.18%) 60		
Ear and labyrinth disorders tinnitus alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	11 / 109 (10.09%) 12		
Eye disorders lacrimation increased alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	16 / 109 (14.68%) 19		
Gastrointestinal disorders constipation alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) diarrhoea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) dyspepsia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) gastritis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) stomatitis alternative dictionary used: MedDRA 16.1	39 / 109 (35.78%) 54 25 / 109 (22.94%) 29 14 / 109 (12.84%) 15 6 / 109 (5.50%) 7 64 / 109 (58.72%) 128		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>25</p> <p>17 / 109 (15.60%)</p>			
<p>vomiting</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>45</p> <p>25 / 109 (22.94%)</p>			
<p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>16</p> <p>11 / 109 (10.09%)</p> <p>rash</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>11</p> <p>8 / 109 (7.34%)</p>			
<p>Renal and urinary disorders</p> <p>proteinuria</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>8</p> <p>7 / 109 (6.42%)</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>14</p> <p>10 / 109 (9.17%)</p> <p>back pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6</p> <p>6 / 109 (5.50%)</p> <p>bone pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>12</p> <p>12 / 109 (11.01%)</p> <p>musculoskeletal pain</p> <p>alternative dictionary used: MedDRA 16.1</p>			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6 / 109 (5.50%)</p> <p>7</p>			
<p>myalgia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6 / 109 (5.50%)</p> <p>10</p>			
<p>pain in extremity</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>7 / 109 (6.42%)</p> <p>9</p>			
<p>Infections and infestations</p> <p>infection</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6 / 109 (5.50%)</p> <p>7</p> <p>nasopharyngitis</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6 / 109 (5.50%)</p> <p>7</p> <p>upper respiratory tract infection</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>8 / 109 (7.34%)</p> <p>10</p>			
<p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>22 / 109 (20.18%)</p> <p>29</p>			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported