Clinical trial results:
An Open-Label, Multicenter, Randomized, Phase 2 Study Evaluating the Safety and Efficacy of Cisplatin and Pemetrexed with or without Cixutumumab as First-Line Therapy in Patients with Advanced Nonsquamous Non-Small Cell Lung Carcinoma

Summary

EudraCT number	2010-024014-60
Trial protocol	DE IT BE
Global end of trial date	10 June 2016

Results information

Result version number	v1 (current)
This version publication date	25 June 2017
First version publication date	25 June 2017

Trial information

Trial identification

Sponsor protocol code	I5A-MC-JAEM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01232452
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 13973

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, 1 877-285-4559,
Scientific contact	Available Mon - Fri, 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly,

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	10 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the hypothesis that cixutumumab given in combination with cisplatin and pemetrexed is superior to cisplatin and pemetrexed as first-line therapy for patients with advanced nonsquamous non-small cell lung carcinoma (NSCLC) as measured by progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in accordance with International Conference on 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	12 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Spain: 13
Worldwide total number of subjects	172
EEA total number of subjects	80

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)	126
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

Completers are those participants who died or had progressive disease (PD).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pemetrexed + Cisplatin + Cixutumumab

Arm description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 plus cixutumumab 20 mg/kg given intravenously (IV) on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 plus cixutumumab 20 mg/kg given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Arm type	Experimental
Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 500 mg/m^2 was given IV on Day 1 of a 21 day cycle for up to 4 cycles.

Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

cisplatin 75 mg/m^2 was given IV on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Investigational medicinal product name	cixutumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg given IV on Day 1 of a 21 day cycle for up to 4 cycles.

Arm title	Pemetrexed + Cisplatin

Arm description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 given IV on Day 1 of a 21 day

cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Arm type	Active comparator
Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 500 mg/m^2 was given IV on Day 1 of a 21 day cycle for up to 4 cycles.

Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 75 mg/m^2 was given IV on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Number of subjects in period 1	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin
Started	87	85
Received at least one dose of study drug	85	81
Completed	48	46
Not completed	39	39
Consent withdrawn by subject	11	8
Physician decision	8	12
Adverse event, non-fatal	17	15
Sponsor Decision	3	1
Protocol entry criterion not met	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Pemetrexed + Cisplatin + Cixutumumab

Reporting group description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 plus cixutumumab 20 mg/kg given intravenously (IV) on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 plus cixutumumab 20 mg/kg given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Reporting group title	Pemetrexed + Cisplatin

Reporting group description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 given IV on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Reporting group values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin	Total
Number of subjects	87	85	172
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	59.5	59.3	
standard deviation	± 9.87	± 9.96	-
Gender categorical Units: Subjects			
Female	33	32	65
Male	54	53	107
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	81	80	161

More than one race	0	0	0
Unknown or Not Reported	4	2	6
Ethnicity Units: Subjects			
Hispanic or Latino	13	24	37
Not Hispanic or Latino	45	33	78
Unknown or Not Reported	29	28	57

End points

End points reporting groups

Reporting group title	Pemetrexed + Cisplatin + Cixutumumab

Reporting group description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 plus cixutumumab 20 mg/kg given intravenously (IV) on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 plus cixutumumab 20 mg/kg given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Reporting group title	Pemetrexed + Cisplatin

Reporting group description:

Induction Treatment: Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 given IV on Day 1 of a 21 day cycle for up to 4 cycles. Two additional cycles of cisplatin may be given (6 cycles total) for participants with significant tumor size reduction, after sponsor approval.

Maintenance Therapy: Pemetrexed 500 mg/m^2 given IV every 21 days until progression of disease, unacceptable toxicity, or another withdrawal criterion is met.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from date of randomization until the date of disease progression, or death from any cause, whichever was first. Disease progression was assessed via Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and defined as at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum longest diameter recorded since the baseline measurements, and/or the appearance of one or more new lesion(s), and/or unequivocal progression of existing nontarget lesions. Participants without documentation for disease progression or death were censored at the date of last tumor assessment. The PFS was estimated following the Kaplan-Meier method.

End point type	Primary

End point timeframe:

Randomization Date to Disease Progression or Death From Any Cause Up to 18.3 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[1]	85[2]		
Units: months				
median (confidence interval 95%)	5.45 (3.88 to 6.05)	5.22 (4.24 to 6.74)		

Notes:

[1] - All randomized participants. 20 participants censored.

[2] - All randomized participants. 21 participants censored.

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Pemetrexed + Cisplatin + Cixutumumab v Pemetrexed + Cisplatin
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.47

Secondary: Percentage of Participants Achieving an Objective Response Rate (ORR)

End point title	Percentage of Participants Achieving an Objective Response Rate (ORR)

End point description:

The ORR is the percentage of all participants with Partial Response (PR) or Complete Response (CR) according to RECIST v1.1. Disease progression was defined as at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum longest diameter recorded since the baseline measurements, and/or the appearance of one or more new lesion(s), and/or unequivocal progression of existing nontarget lesions. ORR is confirmed best overall tumor response of CR and PR. CR was defined as the disappearance of all target and non-target lesions; PR defined as a >30% decrease in the sum of the longest diameters (LD) of the target lesions, taking as reference the baseline sum of the LD.

End point type	Secondary

End point timeframe:

Randomization Date to Disease Progression Up to 18.3 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[3]	85[4]		
Units: percentage of participants				
number (confidence interval 95%)	37.9 (27.7 to 49)	30.6 (21 to 41.5)		

Notes:

[3] - All randomized participants.

[4] - All randomized participants.

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR
Comparison groups	Pemetrexed + Cisplatin v Pemetrexed + Cisplatin + Cixutumumab

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.338
Method	Fisher exact

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time from the date of randomization to the date of death from any cause. If the participant is alive at the end of the follow-up period or is lost to follow-up, OS will be censored on the last date the participant is known to be alive. OS was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Randomization Date to Death From Any Cause Up to 20 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[5]	85[6]		
Units: months				
median (confidence interval 95%)	10.68 (8.74 to 9999)	10.38 (7.43 to 14.39)		

Notes:

[5] - Upper limit was not estimable due to data had insufficient events. 47 participants censored.

[6] - All randomized participants. 39 participants censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is measured by the time measurement criteria are first met for CR/PR until the first date that the criteria for PD is met, or death is objectively documented. DOR was estimated using the Kaplan-Meier method. Disease progression was assessed via RECIST version 1.1, and defined as at least a 20% increase in the sum of the longest recorded since the baseline measurements, and/or the appearance of one or more new lesion(s), and/or unequivocal progression of existing non-target lesions.

End point type	Secondary

End point timeframe:

Time from Response to Disease Progression or Death from Any Cause Up to 20 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[7]	18[8]		
Units: months				
median (confidence interval 95%)	4.9 (4.17 to 6.28)	3.91 (2.92 to 6.41)		

Notes:

[7] - All randomized participants. 10 participants censored.

[8] - All randomized participants. 8 participants censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progressive Disease (TTPS)

End point title	Time to Progressive Disease (TTPS)

End point description:

TTPS was defined as the time from the date of randomization until the date of disease progression. Disease progression was assessed via RECIST version 1.1, and defined as at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum longest diameter recorded since the baseline measurements, and/or the appearance of one or more new lesion(s), and/or unequivocal progression of existing non-target lesions. TTPS was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Randomization Date to disease progression Up to 18.3 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[9]	85[10]		
Units: months				
median (confidence interval 95%)	6.05 (5.32 to 7.79)	6.05 (4.93 to 7.89)		

Notes:

[9] - All randomized participants. 39 participants censored.

[10] - All randomized participants. 36 participants censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Worsening of Symptoms as Measured by Lung Cancer Symptom Scale (LCSS) Score

End point title	Time to Worsening of Symptoms as Measured by Lung Cancer Symptom Scale (LCSS) Score

End point description:

TTPS was defined as the time from the date of randomization until the date of worsening of symptoms as measured by Lung Cancer Symptom Scale (LCSS) score. Symptomatic progression was defined as an increase (worsening) of the Average Symptomatic Burden Index (ASBI) that is, the mean of the six major lung cancer specific symptom scores of the LCSS patient scale - ranging from 0 to 100 where

higher score indicates worst outcome). For each participant, the maximum improvement over baseline score was calculated fore each of the 9 LCSS items, ASBI and LCSS total score. Participants without event are censored at the date of the last LCSS assessment. TTPS was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Time to worsening of symptoms as measured by LCSS score Up to 18.3 Months

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[11]	85[12]		
Units: months				
median (confidence interval 95%)	2.14 (1.54 to 2.99)	4.21 (2.43 to 5.36)		

Notes:

[11] - All randomized participants. 38 participants censored.

[12] - All randomized participants. 46 participants censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Change in Tumor Size (CTS)

End point title	Percentage of Participants With a Change in Tumor Size (CTS)

End point description:

CTS was measured by percentage change of tumor size at the end of Cycle 2 comparing to baseline tumor size.

End point type	Secondary

End point timeframe:

Change from baseline measurement to the end of Cycle 2

End point values	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[13]	85[14]		
Units: Percentage of Participants				
arithmetic mean (standard deviation)	-23.88 (± 18.859)	-16.04 (± 26.143)		

Notes:

[13] - All randomized participants.

[14] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Serum Concentration (Cmax) of Cixutumumab, Cycle 1 (First Infusion) and Cycle 4 (Fourth Infusion)

End point title	Pharmacokinetics (PK): Maximum Serum Concentration (Cmax) of Cixutumumab, Cycle 1 (First Infusion) and Cycle 4 (Fourth Infusion)[15]

End point description:

End point type	Secondary

End point timeframe:

First Infusion: [Prior to Infusion (of Cycle1): 1, 72, 168, 336 hours(hrs) and 504 hrs (i.e. Prior to Infusion of Cycle 2)] and Fourth Infusion; [Prior to Infusion (of Cycle 4),1,24,72,120,168,240,336 hrs and 504 hrs (i.e. Prior to Infusion of Cycle 5)]

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary objective is to assess PK profile of pemetrexed + cisplatin + cixutumumab arm only.

End point values	Pemetrexed + Cisplatin + Cixutumumab			
Subject group type	Reporting group			
Number of subjects analysed	71[16]			
Units: microgram/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
First Infusion (n=71)	481 (± 33)			
Fourth Infusion (n=31)	556 (± 17)			

Notes:

[16] - Participants were randomized to pemetrexed + ciplatin + cixutumumab arm and had evaluable PK data.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics (PD) Markers: Free Insulin-like Growth Factor-I (IGF-I, Total IGF-I, and IGF Binding Proteins (IGFBP-3)

End point title	Pharmacodynamics (PD) Markers: Free Insulin-like Growth Factor-I (IGF-I, Total IGF-I, and IGF Binding Proteins (IGFBP-3)[17]

End point description:

Blood samples for the determination of PD marker concentrations were collected at the specified time points for all participants. Analysis of the following markers include free IGF-I, total IGF-I, and IGFBP-3.

End point type	Secondary

End point timeframe:

Preinfusion, Cycle 2, Cycle 4, Cycle 8, Postinfusion, 30-Day Follow-Up

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary objective is to assess the PD profile of pemetrexed + cisplatin + cixutumumab arm only.

End point values	Pemetrexed + Cisplatin + Cixutumumab			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: Number of Participants				

Notes:

[18] - Zero participants were analyzed due to blood samples were not collected to assess biomarker data.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of Cixutumumab

End point title	Immunogenicity of Cixutumumab[19]

End point description:

End point type	Secondary

End point timeframe:

Preinfusion, Cycle1(C1): 1, 72, 168, 240, 336 hours(hrs); C2 and C3: 1, 168, 336 hrs; C4: 1, 24,72,120,168, 240, 336, 504 hrs, Postinfusion; 30 Day Follow Up

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary objective is to assess the immunogenicity of pemetrexed + cisplatin + cixutumumab arm only.

End point values	Pemetrexed + Cisplatin + Cixutumumab			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: Number of Participants				

Notes:

[20] - Zero participants were analyzed due to no immunogenicity analysis was done and assay never developed

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under the Concentration Time Curve (AUC[0-inf]) of Cixutumumab, Cycle 1 (i.e. First Infusion)

End point title	PK: Area Under the Concentration Time Curve (AUC[0-inf]) of Cixutumumab, Cycle 1 (i.e. First Infusion)[21]

End point description:

End point type	Secondary

End point timeframe:

Prior to Infusion (of Cycle 1), 1, 72, 168, 336 hrs and 504 hrs (i.e. Prior to Infusion of Cycle 2)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The secondary objective is to assess the PK profile of pemetrexed + cisplatin + cixutumumab arm only.

End point values	Pemetrexed + Cisplatin + Cixutumumab			
Subject group type	Reporting group			
Number of subjects analysed	57[22]			
Units: microgram*hour/milliliter (ug*hr/mL)				
geometric mean (geometric coefficient of variation)	73200 (± 35)			

Notes:

[22] - Participants were randomized to pemextrexed + cisplatin + cixutumumab arm and had evaluable PK data.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under the Concentration Time Curve During 1 Dosing Interval (i.e. 504 hr, AUC(0-tau) of Cixutumumab, Cycle 4 (i.e. Fourth Infusion)

End point title	PK: Area Under the Concentration Time Curve During 1 Dosing Interval (i.e. 504 hr, AUC(0-tau) of Cixutumumab, Cycle 4 (i.e. Fourth Infusion)[23]

End point description:

End point type	Secondary

End point timeframe:

Prior to Infusion (of Cycle 4), 1, 24, 72, 120, 168, 240, 336 hrs and 504 hrs (i.e. Prior to Infusion of Cycle 5)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary objective is to assess the PK profile of pemetrexed + cisplatin + cixutumumab arm only.

End point values	Pemetrexed + Cisplatin + Cixutumumab			
Subject group type	Reporting group			
Number of subjects analysed	27[24]			
Units: ug*hr/mL				
geometric mean (geometric coefficient of variation)	79700 (± 30)			

Notes:

[24] - Participants who were randomized to the cixutumumab arm and had evaluable PK data

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:	
I5A-MC-JAEM	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Pemetrexed + Cisplatin + Cixutumumab
Reporting group description: -	
Reporting group title	Pemetrexed + Cisplatin
Reporting group description: -	

Serious adverse events	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 85 (57.65%)	31 / 81 (38.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastases to bone			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
embolism			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
extremity necrosis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematoma			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral arterial occlusive disease			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral artery thrombosis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

venous thrombosis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
osteosynthesis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	9 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malaise			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mucosal inflammation			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiac chest pain			

alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden death			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute respiratory failure			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
epistaxis			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary haemorrhage			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

pulmonary oedema			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
blood bilirubin increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	3 / 85 (3.53%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
white blood cell count decreased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericarditis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral ischaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
nervous system disorder			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral motor neuropathy			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal cord compression			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

transient ischaemic attack			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 85 (7.06%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	8 / 18	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	5 / 81 (6.17%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 85 (4.71%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	2 / 2	1 / 1	
pancytopenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vestibular disorder			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
blindness			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhoidal haemorrhage			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
nausea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophagitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

stomatitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
vomiting			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	8 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			

arthralgia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bone pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
compartment syndrome			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscular weakness			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rhabdomyolysis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
dengue fever			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
empyema			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lobar pneumonia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
lung abscess			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
mucosal infection			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pneumonia klebsiella			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia pneumococcal			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative abscess			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 85 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
septic shock			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 2	2 / 7	
deaths causally related to treatment / all	0 / 1	1 / 3	
streptococcal bacteraemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	4 / 85 (4.71%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 85 (4.71%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperkalaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperuricaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoalbuminaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 85 (97.65%)	79 / 81 (97.53%)	
Vascular disorders			
hypotension			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	8 / 85 (9.41%)	1 / 81 (1.23%)	
occurrences (all)	8	1	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	10 / 85 (11.76%)	9 / 81 (11.11%)	
occurrences (all)	12	30	
chest pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	5 / 81 (6.17%)	
occurrences (all)	3	10	
fatigue			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	36 / 85 (42.35%)	33 / 81 (40.74%)	
occurrences (all)	82	63	
influenza like illness			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	6 / 81 (7.41%)	
occurrences (all)	1	7	
mucosal inflammation			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	12 / 85 (14.12%)	3 / 81 (3.70%)	
occurrences (all)	18	3	
non-cardiac chest pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	6 / 81 (7.41%)	
occurrences (all)	4	6	
oedema peripheral			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	13 / 81 (16.05%)	
occurrences (all)	7	19	
pyrexia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	10 / 81 (12.35%)	
occurrences (all)	5	14	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	13 / 85 (15.29%)	16 / 81 (19.75%)	
occurrences (all)	21	20	
dyspnoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	14 / 85 (16.47%)	16 / 81 (19.75%)	
occurrences (all)	21	26	
epistaxis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	0 / 81 (0.00%)	
occurrences (all)	11	0	
productive cough			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 85 (1.18%)	5 / 81 (6.17%)	
occurrences (all)	1	14	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	3 / 85 (3.53%)	5 / 81 (6.17%)	
occurrences (all)	3	6	
depression			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	4 / 81 (4.94%)	
occurrences (all)	5	4	
insomnia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	7 / 81 (8.64%)	
occurrences (all)	5	10	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	8 / 85 (9.41%)	4 / 81 (4.94%)	
occurrences (all)	11	6	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 85 (4.71%)	5 / 81 (6.17%)	
occurrences (all)	4	7	
blood creatinine increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	12 / 85 (14.12%)	16 / 81 (19.75%)	
occurrences (all)	18	20	
neutrophil count decreased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	9 / 85 (10.59%)	6 / 81 (7.41%)	
occurrences (all)	24	10	
platelet count decreased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 85 (7.06%)	9 / 81 (11.11%)	
occurrences (all)	6	14	
weight decreased			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	17 / 85 (20.00%)	11 / 81 (13.58%)	
occurrences (all)	28	13	
white blood cell count decreased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	4 / 81 (4.94%)	
occurrences (all)	10	6	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	11 / 85 (12.94%)	5 / 81 (6.17%)	
occurrences (all)	13	7	
dysgeusia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	8 / 81 (9.88%)	
occurrences (all)	9	10	
paraesthesia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	33 / 85 (38.82%)	36 / 81 (44.44%)	
occurrences (all)	103	98	
leukopenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 85 (7.06%)	5 / 81 (6.17%)	
occurrences (all)	12	27	
neutropenia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	12 / 85 (14.12%)	17 / 81 (20.99%)	
occurrences (all)	29	35	
thrombocytopenia			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	8 / 85 (9.41%)	5 / 81 (6.17%)	
occurrences (all)	31	9	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	9 / 85 (10.59%)	4 / 81 (4.94%)	
occurrences (all)	11	4	
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	8 / 85 (9.41%)	7 / 81 (8.64%)	
occurrences (all)	8	10	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	4 / 85 (4.71%)	11 / 81 (13.58%)	
occurrences (all)	6	15	
constipation			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	27 / 85 (31.76%)	19 / 81 (23.46%)	
occurrences (all)	39	28	
diarrhoea			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	19 / 85 (22.35%)	16 / 81 (19.75%)	
occurrences (all)	29	21	
dyspepsia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	3 / 81 (3.70%)	
occurrences (all)	5	4	
dysphagia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
nausea			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	45 / 85 (52.94%)	41 / 81 (50.62%)	
occurrences (all)	74	101	
stomatitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	14 / 85 (16.47%)	6 / 81 (7.41%)	
occurrences (all)	24	8	
vomiting			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	29 / 85 (34.12%)	28 / 81 (34.57%)	
occurrences (all)	41	55	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	3 / 81 (3.70%)	
occurrences (all)	8	3	
rash			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	7 / 85 (8.24%)	4 / 81 (4.94%)	
occurrences (all)	7	5	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	9 / 85 (10.59%)	10 / 81 (12.35%)	
occurrences (all)	10	13	
bone pain			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
pain in extremity			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	2 / 81 (2.47%)	
occurrences (all)	6	2	
Infections and infestations			

conjunctivitis			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	3 / 85 (3.53%)	5 / 81 (6.17%)	
occurrences (all)	5	6	
upper respiratory tract infection			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 85 (2.35%)	6 / 81 (7.41%)	
occurrences (all)	2	7	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	24 / 85 (28.24%)	27 / 81 (33.33%)	
occurrences (all)	36	32	
dehydration			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	10 / 85 (11.76%)	6 / 81 (7.41%)	
occurrences (all)	13	8	
hyperglycaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	43 / 85 (50.59%)	16 / 81 (19.75%)	
occurrences (all)	156	45	
hyperkalaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	2 / 81 (2.47%)	
occurrences (all)	8	3	
hypocalcaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	1 / 81 (1.23%)	
occurrences (all)	7	1	
hypokalaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	6 / 85 (7.06%)	4 / 81 (4.94%)	
occurrences (all)	7	4	
hypomagnesaemia			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	9 / 85 (10.59%)	6 / 81 (7.41%)	
occurrences (all)	13	6	
hyponatraemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 85 (5.88%)	4 / 81 (4.94%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2011	The changes made to the protocol were as follows: clarification of inclusion and exclusion criteria clarification of the discontinuation of patients clarification of treatment administration clarification of hyperglycemia assessments clarification of the definition of time to progression disease addition of an interim analysis for safety, after 50 patients complete 2 cycles additional hematology/chemistry assessments during induction (Cycles 1-4) to comply with cisplatin label specification that physical exams will include neurologic assessments to comply with the cisplatin label addition of sampling windows to pharmacokinetics sampling table
22 November 2011	The changes to the protocol were as follows: inclusion of an independent data assessment committee (IDAC) and clarification of the roles of data assessment committee and IDAC modification of glucose inclusion critera and criteria for starting and stopping daily testing adding an option to extend cisplatin therapy through Cycle 6 for qualifying participants (after Sponsor consultation) and corresponding addition of weekly hematology and -chemistry for these participants modification of chemistry sampling in Cycle 1 for all participants -update of compound background information to be consistent with the most recent IB removal of requirement for full local chemistry panel at each central chemistry time point clarification of use and interpretation of central versus local laboratory chemistry data addition of fasting requirements (minimum of 4 hours) prior each chemistry or glucose assessment
09 March 2012	The changes to the protocol were as follows: The level of acceptable efficacy has now been reestimated to be at least 7.16 months.

11 April 2012	The changes to the protocol were as follows: The protocol has been updated to include drug product at a concentration of 15 mg/mL (750 mg/50 mL).
19 February 2013	The changes to the protocol were as follows: Addition of the extension period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported