Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Study of the Safety and Efficacy of Farletuzumab in Combination with a Platinum-Containing Doublet in Chemotherapy-Naive Subjects with Stage IV Adenocarcinoma of the Lung (FLAIR)

Summary

EudraCT number	2010-022229-13
Trial protocol	DE ES IT
Global end of trial date	01 November 2013

Results information

Result version number	v1 (current)
This version publication date	19 May 2016
First version publication date	19 May 2016

Trial information

Trial identification

Sponsor protocol code	MORAb-003-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01218516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Morphotek (subsidiary of Eisai)
Sponsor organisation address	210 Welsh Pool Road, Exton, United States, 19341
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743,
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743,

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	01 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2012
Global end of trial reached?	Yes
Global end of trial date	01 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the effect of farletuzumab versus placebo in combination with either a platinum agent (carboplatin) with paclitaxel or a platinum agent (carboplatin or cisplatin) with pemetrexed followed by farletuzumab or placebo on investigator-assessed progression-free survival (PFS) as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 or definitive clinical disease progression (eg, new occurrence of positive fluid cytology) in chemotherapy-naïve subjects with folate receptoralpha (FRA)-expressing Stage IV adenocarcinoma of the lung.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use (2002).
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 (2013)
- European Clinical Trial Directive 2005/28/EC and European Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Australia: 15

Worldwide total number of subjects	130
EEA total number of subjects	69

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)	89
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All screening procedures were completed within 30 days prior to and including the Cycle 1 Day 1 Visit.

Period 1

Period 1 title	Combination Therapy
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Chemotherapy

Arm description:

During Combination Therapy, placebo was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.

Arm type	Active comparator
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

carboplatin (area under the serum concentration-time curve for a target of 6 mg/mL•min [AUC6])

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

Dosage and administration details:

paclitaxel (200 mg/m2)

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

Dosage and administration details:

pemetrexed (500 mg/m2)

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

Dosage and administration details:

cisplatin (75 mg/m2)

Arm title	Farletuzumab + Chemotherapy

Arm description:

During Combination Therapy, farletuzumab was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.

Arm type	Experimental
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

carboplatin (area under the serum concentration-time curve for a target of 6 mg/mL•min [AUC6])

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

Dosage and administration details:

paclitaxel (200 mg/m2)

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

Dosage and administration details:

pemetrexed (500 mg/m2)

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

Dosage and administration details:

cisplatin (75 mg/m2)

Investigational medicinal product name	Farletuzumab
Investigational medicinal product code	MORAb-003
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg, administered intravenously

Number of subjects in period 1	Placebo + Chemotherapy	Farletuzumab + Chemotherapy
Started	67	63
Completed	38	28
Not completed	29	35
Physician decision	2	2
Treatment With Items Outside Protocol	1	1
Withdrew Consent	-	1
Participant Discontinued Treatment	2	3
Progressive Disease (PD) by RECIST v 1.1	17	15
Death	2	1
Not specified	3	4
Randomized but not Treated	-	1
Toxicity to TA	-	1
Deterioration of Performance Status	-	3
Delay in TA Administration of >=28days	-	3
Chemotherapy Discontinued	2	-

Period 2

Period 2 title	Monotherapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following at least 4 cycles of combination therapy, participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.

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

Dosage and administration details:

7.5 mg/kg, administered intravenously

Arm title	Farletuzumab

Arm description:

Following at least 4 cycles of combination therapy, participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.

Arm type	Experimental
Investigational medicinal product name	Farletuzumab
Investigational medicinal product code	MORAb-003
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5 mg/kg, administered intravenously

Number of subjects in period 2	Placebo	Farletuzumab
Started	38	28
Completed	38	28

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Chemotherapy
Reporting group description:	
During Combination Therapy, placebo was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.	
Reporting group title	Farletuzumab + Chemotherapy
Reporting group description:	
During Combination Therapy, farletuzumab was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.	

Reporting group values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy	Total
Number of subjects	67	63	130
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	61	60	
full range (min-max)	46 to 79	38 to 80	-
Gender categorical			
Units: Subjects			
Female	26	29	55
Male	41	34	75

End points

End points reporting groups

Reporting group title	Placebo + Chemotherapy

Reporting group description:

During Combination Therapy, placebo was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.

Reporting group title	Farletuzumab + Chemotherapy

Reporting group description:

During Combination Therapy, farletuzumab was given with a protocol-approved platinum doublet (either carboplatin/paclitaxel,carboplatin/pemetrexed, or cisplatin/pemetrexed) for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.

Reporting group title	Placebo

Reporting group description:

Following at least 4 cycles of combination therapy, participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.

Reporting group title	Farletuzumab

Reporting group description:

Following at least 4 cycles of combination therapy, participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.

Subject analysis set title	Placebo + Chemotherapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Consists of all randomized subjects who received at least 1 dose of test article (placebo), with treatment assignments designated according to actual study treatment received. This was the primary analysis population for evaluating treatment administration, tolerability, and safety.

Subject analysis set title	Farletuzumab + Chemotherapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Consists of all randomized subjects who received at least 1 dose of test article (farletuzumab), with treatment assignments designated according to actual study treatment received. This was the primary analysis population for evaluating treatment administration, tolerability, and safety.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from the date of randomization to the date of the first observation of investigator-assessed (radiology review) progression based on Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 or other protocol-approved measures of disease progression (eg, new occurrence of positive fluid cytology, newly diagnosed evidence of disease progression from histologic samples, PET-positive metastases, or new bone or brain metastases), or date of death, whatever the cause. Disease progression as assessed by the investigator per RECIST v1.0 was defined as at least a 20% increase in sum of longest diameters (RECIST definition) compared to baseline (or lowest sum while on study if less than baseline), or any new lesions (measurable or nonmeasurable).

End point type	Primary

End point timeframe:

From date of first administration of study drug up to 6 month follow-up from randomization of the last participant i.e. cut-off date 15 Dec 2012 for primary analysis and cut-off date of 1 Nov 2013 or up to approximately 29 months for final analysis.

End point values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: Months				
median (confidence interval 95%)				
Per Primary Analysis Cut-Off Date	5.8 (5 to 6.8)	4.7 (4.2 to 5.6)		
Per Final Analysis Cut-Off Date	5.9 (5 to 7)	4.7 (4.2 to 5.6)		

Statistical analyses

Statistical analysis title	P-value (Per Primary Analysis Cut-Off Date)
Comparison groups	Placebo + Chemotherapy v Farletuzumab + Chemotherapy
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3519
Method	Logrank

Statistical analysis title	P-value (Per Final Analysis Cut-Off Date)
Comparison groups	Placebo + Chemotherapy v Farletuzumab + Chemotherapy
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1555
Method	Logrank

Secondary: Overall Response rate (ORR)

End point title	Overall Response rate (ORR)

End point description:

ORR, defined as the percentage of participants who had best overall response (BOR) of complete response (CR) or partial response (PR) as determined by investigator's radiologic assessments using RECIST 1.1 for target lesions and assessed by Magnetic resonance imaging (MRI) and computerized tomography (CT) scan (for double blind treatment period i.e. Randomization Phase). CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) had to have reduction in short axis to less than 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ORR = CR + PR.

End point type	Secondary

End point timeframe:

From Day 1 until documented radiographic progression, other protocol-approved measures of disease progression, withdrawal by participant, death due to any cause, or cut-off date of 1 Nov 2013 i.e. up to approximately 29 months for final analysis.

End point values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: Percentage of Participants				
number (not applicable)	37.3	41.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR was derived for those participants with objective evidence of CR or PR. DR was defined as the time (in months) from first documentation of objective response (CR or PR) to the first documentation of disease progression (ie, objective tumor progression as assessed by investigator's radiology review or other protocol-approved measures of disease progression) or death due to any cause.

End point type	Secondary

End point timeframe:

From the first documentation of objective response (CR or PR) to the first documentation of disease progression, death due to any cause, or cut-off date of 1 Nov 2013 i.e. up to approximately 29 months for final analysis.

End point values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Months				
median (confidence interval 95%)	6.7 (4.1 to 9.4)	4.1 (3 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time (in months) from the date of randomization to the date of death, regardless of cause.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of death due to any cause or up to cut-off date of 1 Nov 2013 (up to approximately 29 months) for final analysis.

End point values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	63		
Units: Months				
median (confidence interval 95%)	10.5 (8.3 to 14)	14.1 (9.5 to 18.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment emergent adverse events (TEAEs) and Treatment emergent Serious adverse events (SAEs)

End point title	Number of participants with Treatment emergent adverse events (TEAEs) and Treatment emergent Serious adverse events (SAEs)

End point description:

An Adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered with an investigational product. A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose; resulted in death, was life-threatening (i.e., the subject was at a risk of death at the time of the event; this did not include an event that hypothetically might have caused death if it had been more severe), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, or was a congenital abnormality/birth defect. In this study, treatment emergent adverse events (TEAEs) (defined as an AE that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication) were assessed.

End point type	Secondary

End point timeframe:

For each participant, from the first dose till 30 days after the last dose or cut-off date of 1 Nov 2013 i.e. up to approximately 29 months for final analysis.

End point values	Placebo + Chemotherapy	Farletuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	64		
Units: Participants				
number (not applicable)				
TEAEs	62	64		
Treatment emergent SAEs	29	28		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each participant, from the first dose till 30 days after the last dose or cut-off date of 1 Nov 2013 i.e. up to approximately 29 months for final analysis.

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs), defined as an AE that started/increased in severity on/after the first dose of study drug up to 30 days after final dose of study drug. Per the study Statistical Analysis Plan (SAS), the TEAEs presented include serious and non-serious TEAEs. Additionally, serious TEAEs are presented separately.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Placebo + Chemotherapy

Reporting group description:

During Combination Therapy, placebo was given with a protocol-approved platinum doublet for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received placebo as monotherapy until disease progression.

Reporting group title	Farletuzumab + Chemotherapy

Reporting group description:

During Combination Therapy, farletuzumab was given with a protocol-approved platinum doublet for at least 4, but not more than 6, cycles. Participants who experienced clinical benefit from the Combination Therapy entered the Monotherapy phase and received farletuzumab as monotherapy until disease progression.

Serious adverse events	Placebo + Chemotherapy	Farletuzumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 65 (44.62%)	28 / 64 (43.75%)	
number of deaths (all causes)	46	39	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Metastases to meninges			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cancer pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			

subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (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			
Pyrexia			
subjects affected / exposed	0 / 65 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disease Progression			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Localised oedema			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 65 (3.08%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 65 (4.62%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Weight decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysaesthesia			

subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 65 (7.69%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	1 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 65 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			

subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 65 (6.15%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitic infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (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			
Dehydration			
subjects affected / exposed	0 / 65 (0.00%)	3 / 64 (4.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Chemotherapy	Farletuzumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 65 (95.38%)	64 / 64 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	4 / 65 (6.15%)	1 / 64 (1.56%)	
occurrences (all)	5	1	

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 65 (23.08%)	24 / 64 (37.50%)	
occurrences (all)	16	34	
Fatigue			
subjects affected / exposed	29 / 65 (44.62%)	24 / 64 (37.50%)	
occurrences (all)	52	30	
Pyrexia			
subjects affected / exposed	7 / 65 (10.77%)	10 / 64 (15.63%)	
occurrences (all)	9	18	
Mucosal inflammation			
subjects affected / exposed	9 / 65 (13.85%)	7 / 64 (10.94%)	
occurrences (all)	15	7	
Oedema peripheral			
subjects affected / exposed	7 / 65 (10.77%)	7 / 64 (10.94%)	
occurrences (all)	8	10	
Chills			
subjects affected / exposed	3 / 65 (4.62%)	4 / 64 (6.25%)	
occurrences (all)	3	4	
General physical health deterioration			
subjects affected / exposed	1 / 65 (1.54%)	4 / 64 (6.25%)	
occurrences (all)	1	5	
Non-cardiac chest pain			
subjects affected / exposed	1 / 65 (1.54%)	4 / 64 (6.25%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	13 / 65 (20.00%)	14 / 64 (21.88%)	
occurrences (all)	14	18	
Cough			
subjects affected / exposed	13 / 65 (20.00%)	13 / 64 (20.31%)	
occurrences (all)	15	20	

Dyspnoea exertional			
subjects affected / exposed	2 / 65 (3.08%)	7 / 64 (10.94%)	
occurrences (all)	2	8	
Epistaxis			
subjects affected / exposed	4 / 65 (6.15%)	6 / 64 (9.38%)	
occurrences (all)	4	6	
Pleural effusion			
subjects affected / exposed	3 / 65 (4.62%)	5 / 64 (7.81%)	
occurrences (all)	3	6	
Dysphonia			
subjects affected / exposed	2 / 65 (3.08%)	4 / 64 (6.25%)	
occurrences (all)	2	5	
Productive cough			
subjects affected / exposed	1 / 65 (1.54%)	4 / 64 (6.25%)	
occurrences (all)	1	5	
Oropharyngeal pain			
subjects affected / exposed	4 / 65 (6.15%)	3 / 64 (4.69%)	
occurrences (all)	5	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 65 (9.23%)	8 / 64 (12.50%)	
occurrences (all)	7	8	
Anxiety			
subjects affected / exposed	2 / 65 (3.08%)	7 / 64 (10.94%)	
occurrences (all)	4	7	
Confusional state			
subjects affected / exposed	5 / 65 (7.69%)	0 / 64 (0.00%)	
occurrences (all)	5	0	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	4	4	
Blood creatinine increased			
subjects affected / exposed	4 / 65 (6.15%)	2 / 64 (3.13%)	
occurrences (all)	4	2	
Nervous system disorders			

Dizziness			
subjects affected / exposed	6 / 65 (9.23%)	10 / 64 (15.63%)	
occurrences (all)	6	14	
Headache			
subjects affected / exposed	2 / 65 (3.08%)	8 / 64 (12.50%)	
occurrences (all)	2	9	
Paraesthesia			
subjects affected / exposed	9 / 65 (13.85%)	7 / 64 (10.94%)	
occurrences (all)	11	8	
Dysgeusia			
subjects affected / exposed	5 / 65 (7.69%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
Neuropathy peripheral			
subjects affected / exposed	7 / 65 (10.77%)	4 / 64 (6.25%)	
occurrences (all)	7	4	
Polyneuropathy			
subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	4	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 65 (36.92%)	24 / 64 (37.50%)	
occurrences (all)	29	28	
Neutropenia			
subjects affected / exposed	11 / 65 (16.92%)	22 / 64 (34.38%)	
occurrences (all)	19	34	
Thrombocytopenia			
subjects affected / exposed	7 / 65 (10.77%)	8 / 64 (12.50%)	
occurrences (all)	11	9	
Leukopenia			
subjects affected / exposed	3 / 65 (4.62%)	4 / 64 (6.25%)	
occurrences (all)	6	6	
Febrile neutropenia			
subjects affected / exposed	5 / 65 (7.69%)	3 / 64 (4.69%)	
occurrences (all)	5	3	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	1 / 65 (1.54%)	4 / 64 (6.25%)	
occurrences (all)	1	5	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	5 / 65 (7.69%)	3 / 64 (4.69%)	
occurrences (all)	11	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	30 / 65 (46.15%)	31 / 64 (48.44%)	
occurrences (all)	49	45	
Constipation			
subjects affected / exposed	18 / 65 (27.69%)	21 / 64 (32.81%)	
occurrences (all)	32	29	
Diarrhoea			
subjects affected / exposed	17 / 65 (26.15%)	18 / 64 (28.13%)	
occurrences (all)	24	21	
Vomiting			
subjects affected / exposed	17 / 65 (26.15%)	17 / 64 (26.56%)	
occurrences (all)	34	26	
Stomatitis			
subjects affected / exposed	7 / 65 (10.77%)	6 / 64 (9.38%)	
occurrences (all)	11	8	
Dyspepsia			
subjects affected / exposed	2 / 65 (3.08%)	5 / 64 (7.81%)	
occurrences (all)	2	6	
Abdominal pain			
subjects affected / exposed	3 / 65 (4.62%)	4 / 64 (6.25%)	
occurrences (all)	3	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 65 (9.23%)	2 / 64 (3.13%)	
occurrences (all)	6	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 65 (7.69%)	8 / 64 (12.50%)	
occurrences (all)	5	9	
Alopecia			

subjects affected / exposed	6 / 65 (9.23%)	6 / 64 (9.38%)	
occurrences (all)	9	6	
Dry skin			
subjects affected / exposed	4 / 65 (6.15%)	3 / 64 (4.69%)	
occurrences (all)	6	3	
Pruritus			
subjects affected / exposed	4 / 65 (6.15%)	3 / 64 (4.69%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 65 (3.08%)	10 / 64 (15.63%)	
occurrences (all)	2	12	
Back pain			
subjects affected / exposed	10 / 65 (15.38%)	9 / 64 (14.06%)	
occurrences (all)	10	12	
Arthralgia			
subjects affected / exposed	9 / 65 (13.85%)	8 / 64 (12.50%)	
occurrences (all)	10	9	
Myalgia			
subjects affected / exposed	2 / 65 (3.08%)	6 / 64 (9.38%)	
occurrences (all)	6	10	
Musculoskeletal pain			
subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	4	4	
Bone pain			
subjects affected / exposed	5 / 65 (7.69%)	2 / 64 (3.13%)	
occurrences (all)	7	2	
Infections and infestations			
Pneumonia			
subjects affected / exposed	9 / 65 (13.85%)	5 / 64 (7.81%)	
occurrences (all)	9	5	
Upper respiratory tract infection			
subjects affected / exposed	7 / 65 (10.77%)	5 / 64 (7.81%)	
occurrences (all)	7	5	
Urinary tract infection			

subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	4	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 65 (24.62%)	18 / 64 (28.13%)	
occurrences (all)	23	20	
Dehydration			
subjects affected / exposed	3 / 65 (4.62%)	8 / 64 (12.50%)	
occurrences (all)	3	10	
Hypomagnesaemia			
subjects affected / exposed	6 / 65 (9.23%)	8 / 64 (12.50%)	
occurrences (all)	7	9	
Hypokalaemia			
subjects affected / exposed	4 / 65 (6.15%)	5 / 64 (7.81%)	
occurrences (all)	4	6	
Hyponatraemia			
subjects affected / exposed	0 / 65 (0.00%)	5 / 64 (7.81%)	
occurrences (all)	0	5	
Hyperglycaemia			
subjects affected / exposed	7 / 65 (10.77%)	1 / 64 (1.56%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2011	Part B. - Removed the requirement for subjects with wild-type EGFR from the inclusion criteria. - Updated the inclusion criteria to ensure dose would be adjusted for subject's renal function for both carboplatin and cisplatin. - Clarified that subjects who had more than 28 days between doses of farletuzumab or placebo should be discontinued from study treatment. - Clarified Farletuzumab or Placebo Visit; in the event that the dose of chemotherapy was delayed during Combination Therapy, farletuzumab (2.5 mg/kg) or placebo IV would be administered. There were to be no additional farletuzumab or placebo dose modifications. - Updated farletuzumab/placebo dosing during maintenance as Monotherapy 7.5 mg/kg Q3W. Clarified that the dose could be re-calculated more frequently than when weight changed more than 10% per site guidelines. - Clarified that treatment with other nonstudy monoclonal antibodies and tyrosine kinase inhibitors (TKIs) while on study was not allowed; use of granulocyte colony stimulating factors by study subjects was not allowed for prophylaxis. - Clarified that tumor histology would be verified by the site to ensure adenocarcinoma of the lung. EGFR testing would be completed retrospectively if the status was unknown. Deleted the requirement for central pathologist confirmation of histology. - Added central laboratory assessment of tumor expression of FRA for all subjects. Subjects with no FRA expression were excluded from the study. - Clarified that subjects with confirmation of newly diagnosed evidence of disease would discontinue study treatment (Combination Therapy or Monotherapy) but move on to Follow-up; subjects would not discontinue the study.
10 March 2011	Part C. - Removed post-infusion electrocardiogram (ECG); removed laboratory assessment of lactate dehydrogenase and phosphorus. - Emphasized that exploratory biomarker substudy was not compulsory and required additional subject consent. - Corrected the initial infusion rate 0.2 mL/min, progressed at 0.2 mL/min every 5 min to 1 mL/min; suggested the rate of increase 0.2 mL/min every 5 minutes. - Clarified CT/MRI scanning window during all time points; ±7 days. - Clarified the collection of scans when subjects discontinued study treatment without evidence of radiographic or clinical disease progression or study termination by the sponsor. - Clarified data capture during Follow-up as any additional systemic therapy received for Stage IV adenocarcinoma of the lung and survival status. - Clarified other protocol-approved measures of disease progression, and added symptomatic deterioration, as reasons for discontinuation. - Added the definition of Per Protocol Analysis Set; changed the cut-off for PFS primary analysis to 70 events. - Clarified that independent read would be the read of reference for ORR. - Added details of safety analyses by Data and Safety Monitoring Board (DSMB); changed time point to the 12th subject dosed.

10 March 2011	Part A. - Updated the protocol title to reflect the updated protocol design. - Removed the maintenance component of pemetrexed from the Introduction and from the study design as the benefit was not unequivocally proven in multiple clinical studies. Subjects experiencing clinical benefit after at least 4, but no more than 6, cycles of chemotherapy were to go on to receive farletuzumab or placebo monotherapy per their original randomization assignment. - Updated the study design to simplify proof of concept evaluation of farletuzumab with standard of care chemotherapy for Stage IV non-small cell lung cancer (NSCLC), adenocarcinoma. The study would assess PFS after all cycles of chemotherapy were completed. - Removed "docetaxel" and added "cisplatin" as appropriate to reflect the current chemotherapeutic regimens. - Removed the exclusion of EGFR mutations as there was currently no Food and Drug Administration (FDA) approved, universally agreed upon, method of mutation detection. Tumor samples collected in the context of this study would be assayed retrospectively for EGFR mutations by a central laboratory for exploratory purposes only. Therapeutic decisions would not be made based on the EGFR mutation assay developed for the purposes of this clinical study. - Changed the randomization ratio to 1:1 and decreased sample size by 45 subjects to allow data analysis to be performed sooner. The randomization stratification factor was changed from region to chemotherapy regimen to ensure consistency across chemotherapy regimens selected. - Added new exploratory endpoints: red blood cell folate level, homocysteine level, & circulating tumor cells, and associated collections and assessments. - Added a safety analysis specifically aimed at evaluating any significant increase in toxicity or treatment intolerability due to the novel combination of pemetrexed and farletuzumab to the study design. - Updated the number of subjects to be randomized (120).
16 March 2011	- Updated rationales for change in protocol-approved chemotherapy regimen - Deleted the requirement for EGFR wild type - Updated the statistical design.
22 December 2011	Part A. - Additional safety information was added as a result of the ongoing DSMB reviews. - Added the definition of clinical progression throughout to address subjects who have definitive progressive disease (PD) other than by RECIST 1.1. - Deleted PFS after Combination Therapy as a secondary objective; this was now included as part of the primary analysis for PFS. - Changed "disease stabilization" to PFS throughout in correlation analyses since PFS was the primary endpoint and OS was the key secondary endpoint. - Clarified that all doses of farletuzumab, placebo and chemotherapy would be administered on Day 1 of the week specified. - Clarified that the investigator would choose which one of the 3 protocol-approved chemotherapy regimens would be administered to each subject. - Provided the option of administering carboplatin at AUC 5 or 6 as clinically indicated. - Clarified the timing of the DSMB safety review as the first 6 subjects who received farletuzumab in combination with a pemetrexed-containing chemotherapy regimen. - Corrected study duration to be approximately 29 months. - Removed limitation on alkaline phosphatase (ALK-P) from inclusion criteria to allow subjects with bone metastasis to be included. Clarified the definition of surgically sterile.

22 December 2011	Part B. - Clarified timing of the end of palliative radiation in relationship to the first dose of farletuzumab or placebo in the exclusion criteria as being prior to first dose. Clarified the required timing of completion for radiotherapy, surgery, steroid and anticonvulsant treatment completion as being at least 14 days prior to the first dose. Clarified exclusion of "other" immunotherapies with the exception of low-dose steroids. Added exclusion for allergic reaction to "any components of farletuzumab". - Changed serum and urine FRA sampling time point to Cycle 4 Week 1 Day 1. Changed RBC folate and total homocysteine sampling time points to Cycle 1 Week 1 Day 1. - Deleted sampling for serum FRA, urine FRA, RBC folate, total homocysteine, CTC, and biomarkers from the Monotherapy phase. Updated quantities of blood and urine to be collected. - Changed the maximum rate of infusion from 1 mL/min to 2 mL/min, and specified that if 2 mL/min was well tolerated, subsequent infusions could be started at that rate. - Clarified the inclusion of positive fluid cytology as a protocol-approved measure of progression. - Clarified the timing of screening evaluations - Clarified determination of sample size for OS power and provided rationale for same. Added the OS interim futility analysis and clarified the timing for same. Futility considerations were to be based on conditional power with a suggested boundary of 2% (conditional power at estimated effect size), corresponding to an approximate OS HR futility boundary of 1.0. - Instead of an additional secondary endpoint of 'PFS at the end of Chemotherapy', the analysis was presented as part of the primary analysis, but at a pre-specified time point, to eliminate any bias associated with the timing of the completion of the Chemotherapy. - Additional safety monitoring milestones were included, as well as the proposed milestone for an OS futility analysis. -Updated the assay for determination of FRA.
31 January 2013	- The assessment of the primary endpoint (PFS by RECIST v.1.1) was changed from "as assessed by independent central radiology" to "as assessed by investigator review." Originally, the study design called for analysis of PFS based on RECIST v.1.1 assessment by central radiographic review after the 70th event of disease progression or death. Approximately 6 months after the last subject was enrolled, a blinded assessment was performed to assess the extent of discordance between the investigator RECIST assessments and those of the independent central reviewers. Based on these results and on simulations performed to extrapolate the projected timeline to reach the study target of 70 PFS events by independent central review, it became evident that it would likely take significant additional study time, even beyond the projected follow-up for the OS endpoint, to reach this target; in fact, this extrapolation suggested that the target may never be reached with a sample size of 130 subjects. Therefore the primary endpoint was changed to investigator assessment of PFS by RECIST v.1.1, while maintaining the PFS assessment by independent central review as a key sensitivity analysis. - The primary Cox model was changed to an unstratified model so that the estimation and testing methodologies would be consistent. - Switched from an event-driven, independent PFS endpoint (70 events) to a duration driven, investigator-assessed PFS endpoint (minimum of 6 months follow-up).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Results were ready but could not be released before 21 July 2015 due to EudraCT System issues.

Notes: