Clinical trial results:
A Single-Arm, Multicenter, Open-Label, Phase 2 Study of nab®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2016-002071-96
Trial protocol	ES DE GR
Global end of trial date	06 November 2019

Results information

Result version number	v1 (current)
This version publication date	15 November 2020
First version publication date	15 November 2020

Trial information

Trial identification

Sponsor protocol code	I4X-MC-JFCP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02392507
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15529

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 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to determine if nab-paclitaxel and carboplatin chemotherapy plus necitumumab is effective and safe in participants with stage IV squamous non-small cell lung cancer.

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 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	21 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Greece: 8
Worldwide total number of subjects	54
EEA total number of subjects	39

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)	27
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with known best overall response and off study treatment were considered to be completed.

Period 1

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

Arms

Arm title	Necitumumab + Nab-paclitaxel + Carboplatin

Arm description:

Induction: Necitumumab administered intravenously (IV) at 800 milligram (mg) on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 milligram per square meter (mg/m²) on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC (area under curve) 6 milligram per milliliter over time (mg*min/mL) on day 1 of each cycle, for a maximum of 4 cycles. Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).

Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	Necitumumab
Investigational medicinal product code	LY3012211
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Necitumumab administered intravenously (IV) at 800 milligram (mg) on day 1 and 8 of each cycle (3 week cycles).

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle.

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

Dosage and administration details:

Carboplatin administered IV at a concentration of AUC 6 mg*min/mL on day 1 of each cycle, for a maximum of 4 cycles.

Number of subjects in period 1	Necitumumab + Nab-paclitaxel + Carboplatin
Started	54
Received at Least 1 Dose of Study Drug	54
Completed	47
Not completed	7
Adverse event, serious fatal	3
Physician decision	1
Consent withdrawn by subject	2
On Study Treatment at Study Conclusion	1

Period 2

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

Arms

Arm title	Necitumumab + Nab-paclitaxel

Arm description:

Induction: Necitumumab administered intravenously (IV) at 800 milligram (mg) on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 milligram per square meter (mg/m²) on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC (area under curve) 6 milligram per milliliter over time (mg*min/mL) on day 1 of each cycle, for a maximum of 4 cycles. Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).

Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	Necitumumab
Investigational medicinal product code	LY3012211
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle.

Number of subjects in period 2[1]	Necitumumab + Nab-paclitaxel
Started	34
Completed	32
Not completed	2
Adverse event, serious fatal	1
On Study Treatment at Study Conclusion	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: After induction regimen participants with disease response are eligible for maintenance regimen.

Baseline characteristics

Reporting groups	
Reporting group title	Induction Regimen

Reporting group description:

Induction: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC 6 mg*min/mL on day 1 of each cycle, for a maximum of 4 cycles.
Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).
Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group values	Induction Regimen	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.96		
standard deviation	± 7.48	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	42	42	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	50	50	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	53	53	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
United States	15	15	
Germany	4	4	
Spain	27	27	
Greece	8	8	

End points

End points reporting groups

Reporting group title	Necitumumab + Nab-paclitaxel + Carboplatin

Reporting group description:

Induction: Necitumumab administered intravenously (IV) at 800 milligram (mg) on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 milligram per square meter (mg/m²) on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC (area under curve) 6 milligram per milliliter over time (mg*min/mL) on day 1 of each cycle, for a maximum of 4 cycles. Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).

Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Necitumumab + Nab-paclitaxel

Reporting group description:

Induction: Necitumumab administered intravenously (IV) at 800 milligram (mg) on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 milligram per square meter (mg/m²) on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC (area under curve) 6 milligram per milliliter over time (mg*min/mL) on day 1 of each cycle, for a maximum of 4 cycles. Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).

Participants may continue to receive treatment until discontinuation criteria are met.

Subject analysis set title	Necitumumab + Nab-Paclitaxel + Carboplatin
Subject analysis set type	Per protocol

Subject analysis set description:

Induction: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC 6 mg*min/mL on day 1 of each cycle, for a maximum of 4 cycles.
Maintenance: Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles).
Participants may continue to receive treatment until discontinuation criteria are met.

Subject analysis set title	Necitumumab
Subject analysis set type	Per protocol

Subject analysis set description:

Necitumumab administered IV 800 mg on day 1 and 8 of each cycle (3 week cycles).

Subject analysis set title	Carboplatin
Subject analysis set type	Per protocol

Subject analysis set description:

Carboplatin administered IV at a concentration of AUC 6 mg*min/mL on day 1 of each cycle, for a maximum of 4 cycles.

Subject analysis set title	Paclitaxel
Subject analysis set type	Per protocol

Subject analysis set description:

Nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle.

Primary: Percentage of Participants Who Achieve Best Overall Tumor Response of Complete Response or Partial Response (Objective Tumor Response Rate [ORR])

End point title	Percentage of Participants Who Achieve Best Overall Tumor Response of Complete Response or Partial Response (Objective Tumor Response Rate [ORR])[1]

End point description:

ORR was the percentage of participants achieving a best overall response of complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of nontarget lesions, and no appearance of new lesions. Progressive disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with

reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. Analysis population included all randomized participants who received at least 1 dose of study drug and who had a complete radiographic assessment at baseline and at least 1 complete radiographic assessment post-baseline.

End point type	Primary

End point timeframe:

From Date of Randomization to Objective Disease Progression (Up to 18 Months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics were planned or conducted for this endpoint.

End point values	Necitumumab + Nab-paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: percentage of participants				
number (not applicable)	51.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS defined as time from date of randomization until first radiographic documentation of measured PD defined by RECIST v1.1 or death from any cause. PD was at least 20% increase in sum of diameters of target lesions with reference being smallest sum on study and an absolute increase of at least 5 mm,or unequivocal progression of non-target lesions,or 1 or more new lesions.If participant does not have complete baseline disease assessment,PFS time censored at date of randomization,regardless of whether or not objectively determined disease progression or death observed for participant.If participant was not known to have died or have objective progression as of data inclusion cutoff date for analysis,the PFS time censored at last adequate tumor assessment date.The use of new anticancer therapy prior to occurrence of PD resulted in censoring at the date of last radiographic assessment prior to initiation of new therapy. Censored participants = 15.

End point type	Secondary

End point timeframe:

From Date of Randomization to Measured Progressive Disease or Death Due to Any Cause (Up to 18 Months)

End point values	Necitumumab + Nab-paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	54[2]			
Units: Months				
median (confidence interval 95%)	5.59 (4.24 to 7.69)			

Notes:

[2] - Analysis population included all randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS defined as the time from the date of randomization to the date of death due to any cause. Participants who are alive at the time of study completion or are lost to follow-up will be censored at the time they were last known to be alive. Analysis population included all randomized participants who received at least 1 dose of study drug. Censored participants = 35.

End point type	Secondary

End point timeframe:

From Date of Randomization until Death Due to Any Cause (Up to 18 Months)

End point values	Necitumumab + Nab-paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	54[3]			
Units: Months				
median (confidence interval 95%)	15.54 (10.18 to 99999)			

Notes:

[3] - 99999 = NA; The upper limit of the 95% CI was not calculated due to the high censoring rate.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieve Best Overall Disease Response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control Rate [DCR])

End point title	Percentage of Participants Who Achieve Best Overall Disease Response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control Rate [DCR])

End point description:

DCR was percentage of participants with a best overall response of CR,PR, or Stable Disease (SD) as per Response using RECIST v1.1 criteria. CR defined as disappearance of all target and nontarget lesions and no appearance of new lesions. PR defined as at least a 30% decrease in sum of LD of target lesions (taking as reference the baseline sum LD),no progression of non-target lesions, and no appearance of new lesions.SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions,no progression of non-target lesions,and no appearance of new lesions.PD was at least a 20% increase in sum of the diameters of target lesions, with reference being smallest sum on study and absolute increase of at least 5 mm,or unequivocal progression of non-target lesions,or 1 or more new lesions. Analysis population included all randomized participants who received at least 1 dose of

study drug and who had a complete radiographic assessment of baseline.

End point type	Secondary

End point timeframe:

From Date of Randomization to Objective Disease Progression or Start of New Anticancer Therapy (Up to 18 Months)

End point values	Necitumumab + Nab-paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: percentage of participants				
number (not applicable)	78.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab, Nab-Paclitaxel, and Carboplatin

End point title	Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab, Nab-Paclitaxel, and Carboplatin

End point description:

The Cmin is the minimum observed serum/plasma concentration of Necitumumab, Nab-Paclitaxel, and Carboplatin. Analysis population included all randomized participants who received at least 1 dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Cycle 3 and cycle 4: predose

End point values	Necitumumab	Carboplatin	Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	32	3	
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 3	65.2 (± 86.9)	0.131 (± 36)	33.6 (± 393)	
Cycle 4	90 (± 74.9)	0.209 (± 197)	107 (± 313)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Concentration (Cmax) of Necitumumab, Nab-Paclitaxel, and Carboplatin

End point title	PK: Maximum Concentration (Cmax) of Necitumumab, Nab-Paclitaxel, and Carboplatin

End point description:

The Cmax is the maximum observed serum/plasma concentration of Necitumumab, Nab-Paclitaxel, and Carboplatin. Analysis population included all randomized participants who received at least 1 dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Cycle 1, 3 and 4: predose and <15minutes (min) post end-of-infusion

End point values	Necitumumab	Carboplatin	Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	32	37	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	231 (± 27.1)	16.4 (± 22)	343 (± 81.2)	
Cycle 3	291 (± 46.5)	16 (± 26.4)	284 (± 73)	
Cycle 4	277 (± 42.5)	10.5 (± 160)	221 (± 77.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants Developing Anti-drug Antibodies to Necitumumab

End point title	Immunogenicity: Number of Participants Developing Anti-drug Antibodies to Necitumumab

End point description:

A participant was considered to have an anti-drug antibody response if anti-drug antibodies (ADA) were detected at any time point. Analysis population included all randomized participants who received at least 1 dose of study drug and had evaluable data for antibodies.

End point type	Secondary

End point timeframe:

Predose Cycle 1 Through Short Term Follow Up (Up To 18 Months)

End point values	Necitumumab + Nab-paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up to 49 Months

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study drug. Gender specific events only occurring in male or female participants have had the number of participants at risk adjusted accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Necitumumab+Nab-paclitaxel+Carboplatin: Induction Phase

Reporting group description:

Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle (3 week cycles); nab-paclitaxel administered IV at 100 mg/m² on day 1, 8 and 15 of each cycle; carboplatin administered IV at a concentration of AUC 6 mg*min/mL on day 1 of each cycle, for a maximum of 4 cycles. Participants may continue to receive treatment until discontinuation criteria are met.

Reporting group title	Necitumumab+Nab-paclitaxel: Maintenance Phase

Reporting group description:

Necitumumab administered IV at 800 mg on day 1 and 8 of each cycle; nab-paclitaxel administered IV at 100mg/m² on day 1 and 8 of each cycle (3 week cycles). Participants may continue to receive treatment until discontinuation criteria are met.

Serious adverse events	Necitumumab+Nab-paclitaxel+Carboplatin: Induction Phase	Necitumumab+Nab-paclitaxel: Maintenance Phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 54 (33.33%)	5 / 34 (14.71%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
peripheral ischaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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			
death			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 54 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
delirium			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
neutrophil count decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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			
febrile neutropenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	2 / 54 (3.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal perforation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
rash maculo-papular			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
urinary retention			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
pathological fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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			
diverticulitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

pulmonary sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypomagnesaemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 54 (1.85%)	0 / 34 (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	Necitumumab+Nab-paclitaxel+Carboplatin: Induction Phase	Necitumumab+Nab-paclitaxel: Maintenance Phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)	32 / 34 (94.12%)	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	2 / 34 (5.88%)	
occurrences (all)	6	2	
blood cholesterol increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
blood creatinine increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 54 (11.11%)	2 / 34 (5.88%)	
occurrences (all)	8	3	
lymphocyte count decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 54 (11.11%)	6 / 34 (17.65%)	
occurrences (all)	22	12	
neutrophil count decreased			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	32 / 54 (59.26%)	1 / 34 (2.94%)	
occurrences (all)	85	3	
platelet count decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	18 / 54 (33.33%)	2 / 34 (5.88%)	
occurrences (all)	41	2	
weight decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
white blood cell count decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	12 / 54 (22.22%)	1 / 34 (2.94%)	
occurrences (all)	46	1	
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
dysgeusia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	1 / 34 (2.94%)	
occurrences (all)	5	1	
paraesthesia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 54 (1.85%)	5 / 34 (14.71%)	
occurrences (all)	1	12	
peripheral motor neuropathy			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	4 / 54 (7.41%)	3 / 34 (8.82%)	
occurrences (all)	6	9	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	7 / 54 (12.96%)	9 / 34 (26.47%)	
occurrences (all)	9	19	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	35 / 54 (64.81%)	15 / 34 (44.12%)	
occurrences (all)	106	33	
leukopenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	0 / 34 (0.00%)	
occurrences (all)	4	0	
neutropenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	0 / 34 (0.00%)	
occurrences (all)	8	0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	8 / 54 (14.81%)	2 / 34 (5.88%)	
occurrences (all)	15	9	
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	32 / 54 (59.26%)	10 / 34 (29.41%)	
occurrences (all)	75	20	
mucosal inflammation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	8	1	
oedema peripheral			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	6 / 54 (11.11%)	2 / 34 (5.88%)	
occurrences (all)	6	2	
pyrexia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	3 / 34 (8.82%)	
occurrences (all)	4	3	
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	19 / 54 (35.19%)	2 / 34 (5.88%)	
occurrences (all)	25	2	
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	19 / 54 (35.19%)	5 / 34 (14.71%)	
occurrences (all)	36	9	
nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	16 / 54 (29.63%)	2 / 34 (5.88%)	
occurrences (all)	25	2	
stomatitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	7 / 54 (12.96%)	2 / 34 (5.88%)	
occurrences (all)	11	2	
vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	10 / 54 (18.52%)	3 / 34 (8.82%)	
occurrences (all)	14	3	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	7 / 34 (20.59%)	
occurrences (all)	5	8	
dysphonia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	2 / 54 (3.70%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
dyspnoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	12 / 54 (22.22%)	4 / 34 (11.76%)	
occurrences (all)	14	5	
epistaxis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	12 / 54 (22.22%)	1 / 34 (2.94%)	
occurrences (all)	17	5	
haemoptysis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
nasal congestion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 54 (11.11%)	0 / 34 (0.00%)	
occurrences (all)	6	0	
oropharyngeal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
productive cough			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	8 / 54 (14.81%)	1 / 34 (2.94%)	
occurrences (all)	8	1	
dermatitis acneiform			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	16 / 54 (29.63%)	4 / 34 (11.76%)	
occurrences (all)	31	5	
dry skin			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	8 / 54 (14.81%)	5 / 34 (14.71%)	
occurrences (all)	11	5	
nail discolouration			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 54 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	4	
pruritus			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 54 (7.41%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
rash			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	20 / 54 (37.04%)	7 / 34 (20.59%)	
occurrences (all)	59	17	
skin fissures			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	1 / 34 (2.94%)	
occurrences (all)	7	1	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
depression			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
insomnia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	5 / 54 (9.26%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	2 / 34 (5.88%)	
occurrences (all)	5	2	
back pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	2 / 34 (5.88%)	
occurrences (all)	6	3	
muscular weakness			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
musculoskeletal chest pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
myalgia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
pain in extremity			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Infections and infestations			
conjunctivitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 34 (2.94%)	
occurrences (all)	4	3	
nail infection			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 54 (1.85%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
paronychia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 54 (3.70%)	8 / 34 (23.53%)	
occurrences (all)	2	12	
respiratory tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	9 / 54 (16.67%)	6 / 34 (17.65%)	
occurrences (all)	12	8	
urinary tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 54 (5.56%)	3 / 34 (8.82%)	
occurrences (all)	3	4	
vaginal infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[1]	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	13 / 54 (24.07%)	1 / 34 (2.94%)	
occurrences (all)	22	1	
hypoalbuminaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	7 / 54 (12.96%)	1 / 34 (2.94%)	
occurrences (all)	21	1	
hypocalcaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	10 / 54 (18.52%)	1 / 34 (2.94%)	
occurrences (all)	16	3	
hypoglycaemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 54 (1.85%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
hypokalaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	10 / 54 (18.52%)	1 / 34 (2.94%)	
occurrences (all)	14	1	
hypomagnesaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	26 / 54 (48.15%)	9 / 34 (26.47%)	
occurrences (all)	60	42	
hyponatraemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 54 (9.26%)	1 / 34 (2.94%)	
occurrences (all)	9	1	
hypophosphataemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	12 / 54 (22.22%)	3 / 34 (8.82%)	
occurrences (all)	30	38	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Gender specific events only occurring in male or female participants have had the number of participants at risk adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2016	- Changes made to open up the study for European Union (EU) study sites. - Package Leaflet (PL) reference was updated for nab-paclitaxel (abraxane) and carboplatin. - Investigator's Brochure (IB) information was revised based on the necitumumab IB update

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported