Clinical trial results:
Open-label, randomized, controlled, multicenter Phase II study investigating 2 cilengitide regimens in combination with cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine) compared to cetuximab and platinum-based chemotherapy alone as first-line treatment for patients with advanced Non Small Cell Lung Cancer (NSCLC).

Summary

EudraCT number	2008-004148-35
Trial protocol	IE BE DE ES FR IT CZ
Global end of trial date	29 July 2013

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	EMR200037-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00842712
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Str. 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck KGaA, 49 6151-72-5200, service@merckgroup.com
Scientific contact	Communication Centre, Merck KGaA, 49 6151-72-5200, service@merckgroup.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of cilengitide in combination with cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine) compared to cetuximab and platinum-based chemotherapy alone in terms of progression free survival (PFS) time (based on independent assessment, IRC) in the total population (regardless of endothelial growth factor receptor [EGFR] expression) and in the subgroup of subjects with high EGFR expression.

Protection of trial subjects:

In this trial highest medical and ethical standards were followed, in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 35
Country: Number of subjects enrolled	France: 61
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Poland: 37
Worldwide total number of subjects	232
EEA total number of subjects	232

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)	182
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Feb 2009/Jun 2012. Clinical data cut-off: 26 Jun 2013, Study completion date: July 2013.

Pre-assignment

Screening details:

In safety run-in part of study, a total of 12 subjects were enrolled and treated. In randomized part of study, 220 subjects were enrolled and out of these 220 subjects, 215 were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy

Arm description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administed at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 milligram per square meter (mg/m^2) as intravenous infusion over 2 hours on Day 1.

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

Dosage and administration details:

Cisplatin was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1.

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

Dosage and administration details:

Vinorelbine was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8.

Arm title	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy

Arm description:

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m^2 or Cisplatin [Cis] at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine at a dos 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle until progressive disease, death, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

Cisplatin was administered at a dose of 80 mg/m^2 intravenous infusion on Day 1 + Vinorelbine was administered at a dose of 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 of each 3-week cycle along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Arm title	Randomized Part: Cetuximab + Chemotherapy

Arm description:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 was administered as intravenous infusion over

1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

Cisplatin was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine was administered at a dose of 25 mg/m^2 or Cisplatin was administered at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 of each 3-week cycle along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Arm title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem

Arm description:

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m^2) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m^2 intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 milligram per square meter (mg/m^2) as intravenous infusion over 2 hours on Day 1.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin (Cis) was administered at a dose of 75 mg/m^2 as intravenous infusion on Day 1.

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

Dosage and administration details:

Gemcitabine (Gem) was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Arm title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin

Arm description:

Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1

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

Dosage and administration details:

Cisplatin was administered ata dose of 75 mg/m^2 as intravenous infusion on Day 1.

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

Dosage and administration details:

Vinorelbine was administered at a dose of 25 mg/m^2 intravenous infusion on Days 1 and 8 for 3 weeks.

Arm title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem

Arm description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m^2 as intravenous infusion on

Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

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

Dosage and administration details:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1

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

Dosage and administration details:

Cisplatin was administered at dose of 75 mg/m^2 as intravenous infusion on Day 1.

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

Dosage and administration details:

Gem was administered at a dose of 1250 mg/m^2 intravenous infusion on Days 1 and 8 for 3 weeks.

Arm title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin

Arm description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

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

Dosage and administration details:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4.

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

Dosage and administration details:	
Cetuximab was administered at a dose of 400 mg/m^2 intravenous infusion over 2 hours on Day 1.	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Cisplatin was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1.	
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Vinorelbine was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.	

Number of subjects in period 1	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy
Started	85	51	84
Completed	85	50	78
Not completed	0	1	6
Randomized but not treated	-	1	4
Adverse event, non-fatal	-	-	-
Progressive disease	-	-	-
Ongoing at cut-off date	-	-	2

Number of subjects in period 1	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem
Started	3	3	3
Completed	3	1	3
Not completed	0	2	0
Randomized but not treated	-	-	-
Adverse event, non-fatal	-	1	-
Progressive disease	-	1	-
Ongoing at cut-off date	-	-	-

Number of subjects in period 1	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin
Started	3
Completed	2
Not completed	1

Randomized but not treated	-
Adverse event, non-fatal	-
Progressive disease	1
Ongoing at cut-off date	-

Baseline characteristics

Reporting groups

Reporting group title	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administed at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m^2 or Cisplatin [Cis] at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine at a dos 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Randomized Part: Cetuximab + Chemotherapy

Reporting group description:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 was administered as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem

Reporting group description:

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m^2) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m^2 intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

Reporting group title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin

Reporting group description:

Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Reporting group title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem

Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Reporting group title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin

Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Reporting group values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy
Number of subjects	85	51	84
Age categorical Units: Subjects			
Less than 65 years	68	37	66
Greater than or equal to 65 years	17	14	18
Gender categorical Units: Subjects			
Female	34	19	27
Male	51	32	57

Reporting group values	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem
Number of subjects	3	3	3
Age categorical Units: Subjects			
Less than 65 years	3	2	3
Greater than or equal to 65 years	0	1	0
Gender categorical Units: Subjects			
Female	1	0	2
Male	2	3	1

Reporting group values	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin	Total	
Number of subjects	3	232	
Age categorical Units: Subjects			
Less than 65 years	3	182	
Greater than or equal to 65 years	0	50	
Gender categorical Units: Subjects			
Female	2	85	
Male	1	147	

End points

End points reporting groups

Reporting group title	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cilengitide (Cil) was administered at a dose of 2000 mg as intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine (Gem) was administed at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cilengitide (cil) was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] at a dose of 25 mg/m^2 or Cisplatin [Cis] at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine at a dos 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Randomized Part: Cetuximab + Chemotherapy

Reporting group description:

Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab at a dose of 250 mg/m^2 was administered as intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cisplatin [Cis] at a dose of 80 mg/m^2 was administered as intravenous infusion on Day 1 + Vinorelbine [Vin] was administered at a dose of 25 mg/m^2 or Cisplatin at a dose of 75 mg/m^2 was administered as intravenous infusion on Day 1 + Gemcitabine [Gem] at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 of each 3-week cycle) along with Cilengitide and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem

Reporting group description:

Cilengitide (Cil) was administered at a dose of 1000 milligram (mg) as intravenous infusion twice weekly over 1 hour on Days 1 and 4 along with Cetuximab at a dose of 400 milligram per square meter (mg/m^2) as intravenous infusion over 2 hours on Day 1 plus Cisplatin (Cis) 75 mg/m^2 intravenous infusion on Day 1 and Gemcitabine (Gem) at a dose of 1250 mg/m^2 was administered as intravenous infusion on Days 1 and 8 for a period of 3 weeks.

Reporting group title	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin

Reporting group description:

Cilengitide was administered at a dose of 1000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin [Cis] was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Reporting group title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem

Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 75 mg/m^2 as intravenous infusion on Day 1 + Gemcitabine (Gem) was administered at a dose of 1250 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Reporting group title	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin

Reporting group description:

Cilengitide was administered at a dose of 2000 mg as intravenous infusion twice weekly over 1 hour on Days 1 and 4 + Cetuximab was administered at a dose of 400 mg/m^2 as intravenous infusion over 2 hours on Day 1 + Cisplatin (Cis) was administered at a dose of 80 mg/m^2 as intravenous infusion on Day 1 + Vinorelbine (Vin) was administered at a dose of 25 mg/m^2 as intravenous infusion on Days 1 and 8 for 3 weeks.

Primary: Safety run-in Part: Number of subjects with dose limiting toxicities (DLTs)

End point title	Safety run-in Part: Number of subjects with dose limiting toxicities (DLTs)[1][2]

End point description:

The DLT population included all subjects who completed first 3 weeks of treatment (first chemotherapy cycle) or who discontinued treatment due to any DLT during the first 3 weeks of treatment in the safetyrun-in part.

End point type	Primary

End point timeframe:

Up to Week 3

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: The statistical analyses was not planned for this outcome measure.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the safety run-in part of the study as per planned analysis

End point values	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Gem	Safety run-in Part: Cil (1000 mg) + Cetuximab + Cis + Vin	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Gem	Safety run-in Part: Cil (2000 mg) + Cetuximab + Cis + Vin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Subjects				
Independent Read	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Randomized part: Progression free survival (PFS) time - Independent read

End point title	Randomized part: Progression free survival (PFS) time - Independent read[3]

End point description:

The PFS time is defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Independent Read is the assessment of all imaging centrally by an Independent Review Committee (IRC). Intent-to-treat (ITT) population included all participants who were randomized to trial treatment.

End point type	Primary

End point timeframe:

Time from randomization until disease progression, death or last tumor assessment, reported between

day of first subject randomized, that is, Feb 2009 until cut-off date, (26 Jun 2013).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

End point values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	51	84	
Units: Months				
median (confidence interval 95%)	6.2 (5.6 to 7.4)	5.6 (4 to 7.5)	5 (4.2 to 5.6)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0845
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.718
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.492
upper limit	1.048

Secondary: Randomized Part: Progression Free Survival (PFS) Time - Investigator Read

End point title	Randomized Part: Progression Free Survival (PFS) Time - Investigator Read[4]

End point description:

The PFS time is defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Investigator read is the assessment of all imaging by the treating physician at the local trial site. ITT population included all participants who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

Time from randomization until disease progression, death or last tumor assessment, reported between day of first subject randomized, that is, Feb 2009 until cut-off date, (26 Jun 2013).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

End point values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	51	84	
Units: Months				
median (confidence interval 95%)	5.6 (5.4 to 6.7)	5.6 (4.2 to 7)	5.3 (4.2 to 5.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5912
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.909
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.642
upper limit	1.286

Secondary: Randomized Part: Overall Survival (OS) Time

End point title	Randomized Part: Overall Survival (OS) Time[5]

End point description:

The OS time is defined as the time (in months) from randomization to death or last day known to be alive. Subjects without event are censored at the last date known to be alive or at the clinical cut-off date, whatever is earlier. ITT population included all participants who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

Time from randomization until death or last day known to be alive, reported between day of first subject randomized, that is, Feb 2009 until cut-off date,(26 Jun 2013).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

End point values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	51	84	
Units: months				
median (confidence interval 95%)	13.6 (9.5 to 18.6)	13.6 (8.7 to 16.7)	9.7 (7.9 to 13.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy v Randomized Part: Cetuximab + Chemotherapy
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2648
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.813
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.564
upper limit	1.171

Secondary: Randomized Part: Best Overall Response (BOR) Rate

End point title	Randomized Part: Best Overall Response (BOR) Rate[6]

End point description:

The BOR rate is defined as the percentage of subjects having achieved confirmed complete response (CR) or partial response (PR) as the best overall response, based on radiological assessments (based on response evaluation criteria in solid tumors [RECIST]) as assessed by Independent Review Committee (IRC): CR = disappearance of all target lesions; PR = at least 30% decrease in the sum of the longest diameter of target lesions. ITT population included all participants who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

Time from randomization until treatment failure or last tumor assessment, reported between day of first subject randomized, that was, Feb 2009 until cut-off date,(26 Jun 2013)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

End point values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	51	84	
Units: percentage				
number (confidence interval 95%)	37.6 (27.4 to 48.8)	27.5 (15.9 to 41.7)	29.8 (20.3 to 40.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Part: Time to Treatment Failure

End point title	Randomized Part: Time to Treatment Failure[7]

End point description:

Time to treatment failure was defined as the time from first administration of trial treatment until the date of the first occurrence of one of the events defining treatment failure: Progressive Disease (PD) assessed by the investigator, discontinuation of treatment due to PD, discontinuation of treatment due to an adverse event (AE), start of any new anticancer therapy, or withdrawal of consent or death within 60 days of the last tumor assessment or first administration of trial treatment. Time to treatment failure was assessed according to modified World Health Organization (WHO) criteria by Independent Review Committee (IRC). ITT population included all participants who were randomized to trial treatment.

End point type	Secondary

End point timeframe:

Time from randomization until treatment failure or last tumor assessment, reported between day of first subject randomized, that is, Feb 2009 until cut-off date,(26 Jun 2013).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics was reported only for the groups in the randomized part of the study as per planned analysis

End point values	Randomized Part: Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cetuximab + Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	51	84	
Units: months				
median (confidence interval 95%)	4.4 (3.5 to 5.6)	2.8 (1.4 to 4.2)	4.2 (2.8 to 5.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first subject randomized, that was, Feb 2009 until cut-off date (26 Jun 2013)

Adverse event reporting additional description:

The analysis was performed on safety population, defined as all subjects who received any dose of the trial treatment (cilengitide, cetuximab, or chemotherapy), whereby subjects were analyzed according to the actual treatment they received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Cil (Once Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cil 2000 mg intravenous infusion once weekly over 1 hour on Days 1, 8 and 15 of each 3-week cycle + Cetuximab 400 mg/m^2 intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m^2 intravenous infusion on Day 1 + Vin 25 mg/m^2 or Cis 75 mg/m^2 intravenous infusion on Day 1 + Gem 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy

Reporting group description:

Cil 2000 mg intravenous infusion twice weekly over 1 hour on Days 1, 4, 8, 11, 15, and 18 of each 3-week cycle followed by once weekly administration after end of chemotherapy + Cetuximab 400 mg/m^2 intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m^2 intravenous infusion on Day 1 + Vin 25 mg/m^2 or Cis 75 mg/m^2 intravenous infusion on Day 1 + Gem 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Reporting group title	Cetuximab + Chemotherapy

Reporting group description:

Cetuximab 400 mg/m^2 intravenous infusion over 2 hours on Day 1 of Cycle 1 followed by cetuximab 250 mg/m^2 intravenous infusion over 1 hour once weekly on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of all subsequent cycles until progressive disease, death, unacceptable toxicity, or consent withdrawal. Chemotherapy (Cis 80 mg/m^2 intravenous infusion on Day 1 + Vin 25 mg/m^2 or Cis 75 mg/m^2 intravenous infusion on Day 1 + Gem 1250 mg/m^2 intravenous infusion on Days 1 and 8 of each 3-week cycle) was administered along with Cil and cetuximab as per Investigator's discretion up to a maximum of 6 cycles.

Serious adverse events	Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Cetuximab + Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 85 (49.41%)	29 / 50 (58.00%)	45 / 80 (56.25%)
number of deaths (all causes)	56	39	58
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO MENINGES			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
TUMOUR EMBOLISM			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
AORTIC THROMBOSIS			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIAL DISORDER			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIAL THROMBOSIS LIMB			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AXILLARY VEIN THROMBOSIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			

subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOVOLAEMIC SHOCK			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL EMBOLISM			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHOCK			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SUBCLAVIAN VEIN THROMBOSIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPERIOR VENA CAVA SYNDROME			

subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOSIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENA CAVA THROMBOSIS			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISEASE PROGRESSION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
FATIGUE			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	4 / 85 (4.71%)	1 / 50 (2.00%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	1 / 4	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
IMPAIRED HEALING			

subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALAISE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MEDICAL DEVICE COMPLICATION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	4 / 85 (4.71%)	5 / 50 (10.00%)	8 / 80 (10.00%)
occurrences causally related to treatment / all	3 / 4	1 / 5	1 / 8
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
PULMONARY THROMBOSIS			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			

subjects affected / exposed	0 / 85 (0.00%)	2 / 50 (4.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FAILURE TO ANASTOMOSE			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	2 / 85 (2.35%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LIMB INJURY			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPLENIC RUPTURE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARRHYTHMIA SUPRAVENTRICULAR			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STRESS CARDIOMYOPATHY			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR TACHYCARDIA			

subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CENTRAL NERVOUS SYSTEM LESION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 85 (0.00%)	2 / 50 (4.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMA			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CONVULSION			
subjects affected / exposed	2 / 85 (2.35%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STATUS EPILEPTICUS			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 85 (3.53%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	4 / 85 (4.71%)	1 / 50 (2.00%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	3 / 4	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	4 / 80 (5.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
HYPOACUSIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

PERIORBITAL OEDEMA			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			

subjects affected / exposed	1 / 85 (1.18%)	2 / 50 (4.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCTITIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	2 / 85 (2.35%)	1 / 50 (2.00%)	4 / 80 (5.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHITIS			

subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
NAIL BED INFECTION			

subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	4 / 80 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
PNEUMONIA BACTERIAL			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROTEUS INFECTION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 85 (0.00%)	2 / 50 (4.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 85 (1.18%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SKIN INFECTION			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			

subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cil (Once Weekly) + Cetuximab + Chemotherapy	Randomized Part: Cil (Twice Weekly) + Cetuximab + Chemotherapy	Cetuximab + Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 85 (98.82%)	48 / 50 (96.00%)	78 / 80 (97.50%)
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	5 / 85 (5.88%)	1 / 50 (2.00%)	0 / 80 (0.00%)
occurrences (all)	5	1	0
HYPERTENSION			
subjects affected / exposed	9 / 85 (10.59%)	6 / 50 (12.00%)	5 / 80 (6.25%)
occurrences (all)	9	6	5
HYPOTENSION			

subjects affected / exposed	1 / 85 (1.18%)	4 / 50 (8.00%)	4 / 80 (5.00%)
occurrences (all)	1	4	4
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	20 / 85 (23.53%)	15 / 50 (30.00%)	23 / 80 (28.75%)
occurrences (all)	20	15	23
CHEST PAIN			
subjects affected / exposed	5 / 85 (5.88%)	5 / 50 (10.00%)	2 / 80 (2.50%)
occurrences (all)	5	5	2
CHILLS			
subjects affected / exposed	2 / 85 (2.35%)	3 / 50 (6.00%)	2 / 80 (2.50%)
occurrences (all)	2	3	2
FATIGUE			
subjects affected / exposed	29 / 85 (34.12%)	13 / 50 (26.00%)	19 / 80 (23.75%)
occurrences (all)	29	13	19
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 85 (2.35%)	0 / 50 (0.00%)	4 / 80 (5.00%)
occurrences (all)	2	0	4
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	5 / 85 (5.88%)	2 / 50 (4.00%)	2 / 80 (2.50%)
occurrences (all)	5	2	2
OEDEMA PERIPHERAL			
subjects affected / exposed	5 / 85 (5.88%)	5 / 50 (10.00%)	5 / 80 (6.25%)
occurrences (all)	5	5	5
PYREXIA			
subjects affected / exposed	8 / 85 (9.41%)	14 / 50 (28.00%)	15 / 80 (18.75%)
occurrences (all)	8	14	15
XEROSIS			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	4 / 80 (5.00%)
occurrences (all)	0	1	4
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	13 / 85 (15.29%)	11 / 50 (22.00%)	12 / 80 (15.00%)
occurrences (all)	13	11	12
DYSPHONIA			

subjects affected / exposed	2 / 85 (2.35%)	2 / 50 (4.00%)	5 / 80 (6.25%)
occurrences (all)	2	2	5
DYSPNOEA			
subjects affected / exposed	11 / 85 (12.94%)	6 / 50 (12.00%)	5 / 80 (6.25%)
occurrences (all)	11	6	5
DYSPNOEA EXERTIONAL			
subjects affected / exposed	9 / 85 (10.59%)	10 / 50 (20.00%)	7 / 80 (8.75%)
occurrences (all)	9	10	7
EPISTAXIS			
subjects affected / exposed	10 / 85 (11.76%)	10 / 50 (20.00%)	13 / 80 (16.25%)
occurrences (all)	10	10	13
HAEMOPTYSIS			
subjects affected / exposed	3 / 85 (3.53%)	4 / 50 (8.00%)	7 / 80 (8.75%)
occurrences (all)	3	4	7
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	5 / 80 (6.25%)
occurrences (all)	0	1	5
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	4 / 85 (4.71%)	4 / 50 (8.00%)	9 / 80 (11.25%)
occurrences (all)	4	4	9
DEPRESSION			
subjects affected / exposed	3 / 85 (3.53%)	2 / 50 (4.00%)	4 / 80 (5.00%)
occurrences (all)	3	2	4
INSOMNIA			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	9 / 80 (11.25%)
occurrences (all)	4	3	9
HAEMATURIA			
subjects affected / exposed	0 / 85 (0.00%)	3 / 50 (6.00%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 85 (7.06%)	1 / 50 (2.00%)	1 / 80 (1.25%)
occurrences (all)	6	1	1
BLOOD CREATININE INCREASED			

subjects affected / exposed	3 / 85 (3.53%)	5 / 50 (10.00%)	5 / 80 (6.25%)
occurrences (all)	3	5	5
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	5 / 85 (5.88%)	0 / 50 (0.00%)	4 / 80 (5.00%)
occurrences (all)	5	0	4
HAEMOGLOBIN DECREASED			
subjects affected / exposed	8 / 85 (9.41%)	7 / 50 (14.00%)	8 / 80 (10.00%)
occurrences (all)	8	7	8
PLATELET COUNT DECREASED			
subjects affected / exposed	5 / 85 (5.88%)	1 / 50 (2.00%)	3 / 80 (3.75%)
occurrences (all)	5	1	3
WEIGHT DECREASED			
subjects affected / exposed	9 / 85 (10.59%)	3 / 50 (6.00%)	15 / 80 (18.75%)
occurrences (all)	9	3	15
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	6 / 85 (7.06%)	1 / 50 (2.00%)	3 / 80 (3.75%)
occurrences (all)	6	1	3
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	1 / 85 (1.18%)	3 / 50 (6.00%)	1 / 80 (1.25%)
occurrences (all)	1	3	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	8 / 85 (9.41%)	4 / 50 (8.00%)	2 / 80 (2.50%)
occurrences (all)	8	4	2
DYSGEUSIA			
subjects affected / exposed	7 / 85 (8.24%)	4 / 50 (8.00%)	5 / 80 (6.25%)
occurrences (all)	7	4	5
HEADACHE			
subjects affected / exposed	9 / 85 (10.59%)	6 / 50 (12.00%)	6 / 80 (7.50%)
occurrences (all)	9	6	6
NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 85 (1.18%)	3 / 50 (6.00%)	1 / 80 (1.25%)
occurrences (all)	1	3	1
PARAESTHESIA			

subjects affected / exposed	3 / 85 (3.53%)	1 / 50 (2.00%)	8 / 80 (10.00%)
occurrences (all)	3	1	8
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	33 / 85 (38.82%)	22 / 50 (44.00%)	24 / 80 (30.00%)
occurrences (all)	33	22	24
LEUKOPENIA			
subjects affected / exposed	20 / 85 (23.53%)	7 / 50 (14.00%)	10 / 80 (12.50%)
occurrences (all)	20	7	10
LYMPHOPENIA			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	4 / 80 (5.00%)
occurrences (all)	4	3	4
NEUTROPENIA			
subjects affected / exposed	43 / 85 (50.59%)	22 / 50 (44.00%)	35 / 80 (43.75%)
occurrences (all)	46	22	35
THROMBOCYTOPENIA			
subjects affected / exposed	29 / 85 (34.12%)	17 / 50 (34.00%)	24 / 80 (30.00%)
occurrences (all)	29	17	24
THROMBOCYTOSIS			
subjects affected / exposed	3 / 85 (3.53%)	4 / 50 (8.00%)	1 / 80 (1.25%)
occurrences (all)	3	4	1
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	1 / 85 (1.18%)	3 / 50 (6.00%)	6 / 80 (7.50%)
occurrences (all)	1	3	6
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	10 / 85 (11.76%)	7 / 50 (14.00%)	5 / 80 (6.25%)
occurrences (all)	10	7	5
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	7 / 85 (8.24%)	2 / 50 (4.00%)	6 / 80 (7.50%)
occurrences (all)	7	2	6
ABDOMINAL PAIN UPPER			
subjects affected / exposed	7 / 85 (8.24%)	5 / 50 (10.00%)	6 / 80 (7.50%)
occurrences (all)	7	5	6
CONSTIPATION			

subjects affected / exposed	17 / 85 (20.00%)	14 / 50 (28.00%)	19 / 80 (23.75%)
occurrences (all)	17	14	19
DIARRHOEA			
subjects affected / exposed	22 / 85 (25.88%)	14 / 50 (28.00%)	22 / 80 (27.50%)
occurrences (all)	22	14	19
DYSPEPSIA			
subjects affected / exposed	4 / 85 (4.71%)	5 / 50 (10.00%)	2 / 80 (2.50%)
occurrences (all)	4	5	2
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 85 (0.00%)	3 / 50 (6.00%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
HAEMORRHOIDS			
subjects affected / exposed	2 / 85 (2.35%)	4 / 50 (8.00%)	1 / 80 (1.25%)
occurrences (all)	2	4	1
NAUSEA			
subjects affected / exposed	50 / 85 (58.82%)	27 / 50 (54.00%)	42 / 80 (52.50%)
occurrences (all)	50	27	42
STOMATITIS			
subjects affected / exposed	15 / 85 (17.65%)	10 / 50 (20.00%)	11 / 80 (13.75%)
occurrences (all)	15	10	11
VOMITING			
subjects affected / exposed	18 / 85 (21.18%)	14 / 50 (28.00%)	23 / 80 (28.75%)
occurrences (all)	18	14	23
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	19 / 85 (22.35%)	11 / 50 (22.00%)	17 / 80 (21.25%)
occurrences (all)	19	11	17
ALOPECIA			
subjects affected / exposed	13 / 85 (15.29%)	7 / 50 (14.00%)	9 / 80 (11.25%)
occurrences (all)	13	7	9
DERMATITIS ACNEIFORM			
subjects affected / exposed	17 / 85 (20.00%)	7 / 50 (14.00%)	16 / 80 (20.00%)
occurrences (all)	17	7	16
DRY SKIN			

subjects affected / exposed	13 / 85 (15.29%)	5 / 50 (10.00%)	9 / 80 (11.25%)
occurrences (all)	13	5	9
ERYTHEMA			
subjects affected / exposed	1 / 85 (1.18%)	5 / 50 (10.00%)	4 / 80 (5.00%)
occurrences (all)	1	5	4
NAIL TOXICITY			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	1 / 80 (1.25%)
occurrences (all)	4	3	1
PRURITUS			
subjects affected / exposed	7 / 85 (8.24%)	6 / 50 (12.00%)	3 / 80 (3.75%)
occurrences (all)	7	6	3
RASH			
subjects affected / exposed	35 / 85 (41.18%)	17 / 50 (34.00%)	29 / 80 (36.25%)
occurrences (all)	35	17	29
SKIN FISSURES			
subjects affected / exposed	6 / 85 (7.06%)	2 / 50 (4.00%)	6 / 80 (7.50%)
occurrences (all)	6	2	6
SKIN TOXICITY			
subjects affected / exposed	10 / 85 (11.76%)	8 / 50 (16.00%)	7 / 80 (8.75%)
occurrences (all)	10	8	7
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	4 / 85 (4.71%)	4 / 50 (8.00%)	1 / 80 (1.25%)
occurrences (all)	4	4	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 85 (2.35%)	1 / 50 (2.00%)	5 / 80 (6.25%)
occurrences (all)	2	1	5
BACK PAIN			
subjects affected / exposed	13 / 85 (15.29%)	8 / 50 (16.00%)	8 / 80 (10.00%)
occurrences (all)	13	8	8
MUSCLE SPASMS			
subjects affected / exposed	2 / 85 (2.35%)	4 / 50 (8.00%)	2 / 80 (2.50%)
occurrences (all)	2	4	2
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	2 / 85 (2.35%)	1 / 50 (2.00%)	4 / 80 (5.00%)
occurrences (all)	2	1	4
MUSCULOSKELETAL PAIN			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	4 / 80 (5.00%)
occurrences (all)	4	3	4
PAIN IN EXTREMITY			
subjects affected / exposed	10 / 85 (11.76%)	3 / 50 (6.00%)	6 / 80 (7.50%)
occurrences (all)	10	3	6
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	3 / 85 (3.53%)	3 / 50 (6.00%)	5 / 80 (6.25%)
occurrences (all)	3	3	5
FOLLICULITIS			
subjects affected / exposed	2 / 85 (2.35%)	5 / 50 (10.00%)	5 / 80 (6.25%)
occurrences (all)	2	5	5
NASOPHARYNGITIS			
subjects affected / exposed	5 / 85 (5.88%)	5 / 50 (10.00%)	7 / 80 (8.75%)
occurrences (all)	5	5	7
PARONYCHIA			
subjects affected / exposed	14 / 85 (16.47%)	1 / 50 (2.00%)	8 / 80 (10.00%)
occurrences (all)	14	1	8
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	4 / 80 (5.00%)
occurrences (all)	0	0	14
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	30 / 85 (35.29%)	13 / 50 (26.00%)	21 / 80 (26.25%)
occurrences (all)	30	13	21
HYPERKALAEMIA			
subjects affected / exposed	2 / 85 (2.35%)	3 / 50 (6.00%)	3 / 80 (3.75%)
occurrences (all)	2	3	3
HYPOCALCAEMIA			
subjects affected / exposed	6 / 85 (7.06%)	3 / 50 (6.00%)	6 / 80 (7.50%)
occurrences (all)	6	3	6
HYPOKALAEMIA			

subjects affected / exposed	11 / 85 (12.94%)	5 / 50 (10.00%)	7 / 80 (8.75%)
occurrences (all)	11	5	7
HYPOMAGNESAEMIA			
subjects affected / exposed	18 / 85 (21.18%)	10 / 50 (20.00%)	7 / 80 (8.75%)
occurrences (all)	18	10	7
HYPONATRAEMIA			
subjects affected / exposed	6 / 85 (7.06%)	1 / 50 (2.00%)	2 / 80 (2.50%)
occurrences (all)	6	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 December 2008	To be compliant with the suggestions of health authorities: Additional exclusion criteria due to contra-indications and precautions included in the approved summary of product characteristics of vinorelbine, gemcitabine, and cisplatin were included, the safety monitoring of hematological and biochemistry parameters during the safety run-in part of the protocol were intensified to rule out the synergistic toxicities. The sequence of administration of the platinum-based chemotherapy (cisplatin, vinorelbine, and gemcitabine) was corrected to comply with the summary of product characteristics information.
25 November 2009	As per this amendment, the final dose of cilengitide for the randomized part of the study will be increased to 2000 mg/m^2 after the safety run-in part has been completed. The dose of gemcitabine will be increased from 1000 mg/m^2 on day 1 and 8 to the standard label dose of 1250 mg/m^2 gemcitabine on day 1 and 8, additional cardiac safety monitoring would be implemented, changes in the exclusion criteria with respect to partial thromboplastin time, addition of exclusion criteria pertaining to concurrent chronic immunosuppressive or hormone anti-cancer therapy, decreasing timepoints for the collection of circulating endothelial cells or circulating tumor cells, to update safety information of cetuximab and cilengitide.
20 December 2010	The purpose of this amendment was to adjust the sample size and number of study centers, to stop randomizing subjects to Group B on cilengitide 2000 mg twice weekly in combination with cetuximab and platinum-based chemotherapy, a pre-screening visit was added for the assessment of EGFR expression by immunohistochemistry and selective recruitment of subjects with high epidermal growth factor receptor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported