Clinical trial results:
A Randomized, Phase II, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab (MetMab) in Combination with Either Bevacizumab + Platinum + Paclitaxel or Pemetrexed + Platinum as First-Line Treatment in Patients with Stage IIIb or IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2011-003719-42
Trial protocol	DE GB ES LV IT
Global end of trial date	03 November 2015

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	29 June 2016

Trial information

Trial identification

Sponsor protocol code	GO27821

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01496742
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann La Roche AG, +41 61 6878333, global.trial_information@roche.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	03 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of onartuzumab compared with placebo in participants with non-squamous NSCLC in the first-line settiing, as measured by investigator-assessed progression free survival (PFS) in each of two combination treatment cohorts:
Cohort 1: Onartuzumab + bevacizumab + platinum + paclitaxel (Onartuzumab arm) versus (vs.) placebo + bevacizumab + platinum + paclitaxel (Placebo arm)
Cohort 2: Onartuzumab + platinum + pemetrexed (Onartuzumab arm) vs. placebo + platinum + pemetrexed (Placebo arm)

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2012
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	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Philippines: 11
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	259
EEA total number of subjects	117

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)	147
From 65 to 84 years	110
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening period was up to 28 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent

Arm description:

Induction phase: participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 milligrams per square meter (mg/m^2) IV infusion followed by carboplatin (area under the concentration curve [AUC] 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	RO5490258
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received onartuzumab 15 mg/kg IV infusion on Day 1 of every 21-day cycle. First infusion received over 60 minutes and then over 30 minutes from second infusion onward.

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

Dosage and administration details:

Participants received bevacizumab 15 mg/kg IV infusion over 30-90 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received paclitaxel 200 mg/m^2 IV infusion over 3 hours on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received carboplatin AUC 6 IV infusion over 30-60 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received cisplatin 75 mg/m^2 IV infusion over 1-2 hours on Day 1 of every 21-day cycle.

Arm title	Placebo+Bevacizumab+Paclitaxel+Platinum Agent

Arm description:

Induction phase: participants received placebo IV infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

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

Dosage and administration details:

Participants received placebo matched to onartuzumab infusion on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received bevacizumab 15 mg/kg IV infusion over 30-90 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received paclitaxel 200 mg/m^2 IV infusion over 3 hours on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received carboplatin AUC 6 IV infusion over 30-60 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received cisplatin 75 mg/m^2 IV infusion over 1-2 hours on Day 1 of every 21-day cycle.

Arm title	Onartuzumab+Pemetrexed+Platinum Agent

Arm description:

Induction phase: participants received onartuzumab 15 mg/kg IV infusion followed by pemetrexed 500 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	RO5490258
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received onartuzumab 15 mg/kg IV infusion on Day 1 of every 21-day cycle. First infusion received over 60 minutes and then over 30 minutes from second infusion onward.

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

Dosage and administration details:

Participants received pemetrexed 500 mg/m^2 IV infusion over 10 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received carboplatin AUC 6 IV over 30-60 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received cisplatin 75 mg/m^2 IV over 1-2 hours on Day 1 of every 21-day cycle.

Arm title	Placebo+Pemetrexed+Platinum Agent

Arm description:

Induction phase: participants received placebo infusion followed by pemetrexed 500 mg/m^2 IV

infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

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

Dosage and administration details:

Participants received placebo matched to onartuzumab infusion on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received pemetrexed 500 mg/m^2 IV infusion over 10 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received carboplatin AUC 6 IV over 30-60 minutes on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received cisplatin 75 mg/m^2 IV over 1-2 hours on Day 1 of every 21-day cycle.

Number of subjects in period 1	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+Pemetrexed+Platinum Agent
Started	69	70	59
Completed	0	0	0
Not completed	69	70	59
Consent withdrawn by subject	5	5	6
Death	32	29	37
Sponsor decision	29	33	15
Progressive disease	3	2	1
Lost to follow-up	-	1	-

Protocol deviation	-	-	-

Number of subjects in period 1	Placebo+Pemetrexed+Platinum Agent
Started	61
Completed	0
Not completed	61
Consent withdrawn by subject	2
Death	36
Sponsor decision	20
Progressive disease	1
Lost to follow-up	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 milligrams per square meter (mg/m^2) IV infusion followed by carboplatin (area under the concentration curve [AUC] 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received placebo IV infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Onartuzumab+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 mg/kg IV infusion followed by pemetrexed 500 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received placebo infusion followed by pemetrexed 500 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group values	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+Pemetrexed+Platinum Agent
Number of subjects	69	70	59
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean	60.8	59.6	64.5

standard deviation	± 10.6	± 11	± 7.9

Gender categorical Units: Subjects			
Female	22	36	26
Male	47	34	33

Reporting group values	Placebo+Pemetrexed+Platinum Agent	Total	
Number of subjects	61	259	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	62.5		
standard deviation	± 8.9	-	
Gender categorical Units: Subjects			
Female	35	119	
Male	26	140	

End points reporting groups

Reporting group title	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 milligrams per kilogram (mg/kg) intravenous (IV) infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 milligrams per square meter (mg/m^2) IV infusion followed by carboplatin (area under the concentration curve [AUC] 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received placebo IV infusion followed by bevacizumab 15 mg/kg IV infusion followed by paclitaxel 200 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and bevacizumab 15 mg/kg IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Onartuzumab+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 mg/kg IV infusion followed by pemetrexed 500 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received placebo infusion followed by pemetrexed 500 mg/m^2 IV infusion followed by carboplatin (AUC 6 IV) infusion or cisplatin (75 mg/m^2 IV) infusion on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and pemetrexed 500 mg/m^2 IV infusion on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Subject analysis set title	Onartuzumab participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received onartuzumab were included in this group.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time between the date of randomization and the date of the first documented disease progression or death, whichever occurred first. Progressive disease (PD): At least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered

progression. All randomized participants were included in analysis of this end point.

End point type	Primary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until disease progression or death (up to approximately 20 months)

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	59	61
Units: months				
median (confidence interval 95%)	5 (4.7 to 6.9)	6.8 (4.9 to 8.8)	4.9 (4.4 to 5.9)	5.1 (4.6 to 7)

Statistical analyses

Statistical analysis title	Statistical analysis I

Statistical analysis description:

Stratified analysis is reported. The stratification factor is MET IHC status (positive versus negative). Hazard ratios were estimated by Cox regression.

Comparison groups	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent v Placebo+Bevacizumab+Paclitaxel+Platinum Agent
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3327
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.95

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Stratified analysis is reported. The stratification factor is MET IHC status (positive versus negative). Hazard ratios were estimated by Cox regression.

Comparison groups	Placebo+Pemetrexed+Platinum Agent v Onartuzumab+Pemetrexed+Platinum Agent

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3286
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.86

Primary: PFS in Subgroup of Participants with MET Diagnostic Positive Tumors

End point title	PFS in Subgroup of Participants with MET Diagnostic Positive Tumors

End point description:

PFS was defined as the time between the date of randomization and the date of the first documented disease progression or death, whichever occurred first. PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. MET diagnostic-positive population included all randomized participants with MET immunohistochemistry (IHC) score of 2+ or 3+.

End point type	Primary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until disease progression or death (up to approximately 20 months)

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	44	36	37
Units: months				
median (confidence interval 95%)	4.8 (3.7 to 6.2)	6.9 (4.9 to 10.9)	5 (4.5 to 6)	5 (3.7 to 7.2)

Statistical analyses

Statistical analysis title	Statistical analysis I
Comparison groups	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent v Placebo+Bevacizumab+Paclitaxel+Platinum Agent

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0576
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	3.02

Statistical analysis title	Statistical analysis II
Comparison groups	Onartuzumab+Pemetrexed+Platinum Agent v Placebo+Pemetrexed+Platinum Agent
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4271
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.15

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from date of randomization until death from any cause. All randomized participants were included in analysis of this end point. Median OS time was not estimated for "Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent" treatment arm and was reported as 99999. The upper confidence interval was reported as "99999" wherever it was not estimable.

End point type	Secondary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until death (up to approximately 20 months)

End point values	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	70	59	61
Units: months				
median (confidence interval 95%)	99999 (8.1 to 99999)	16.5 (8.8 to 16.5)	8.5 (6.8 to 13.2)	13.7 (6.6 to 99999)

Statistical analyses

Statistical analysis title	Statistical analysis I
Statistical analysis description:	
Stratified analysis is reported. The stratification factor is MET IHC status (positive versus negative). Hazard ratios were estimated by Cox regression.	
Comparison groups	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent v Placebo+Bevacizumab+Paclitaxel+Platinum Agent
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3523
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.48

Statistical analysis title	Statistical analysis II
Statistical analysis description:	
Stratified analysis is reported. The stratification factor is MET IHC status (positive versus negative). Hazard ratios were estimated by Cox regression.	
Comparison groups	Onartuzumab+Pemetrexed+Platinum Agent v Placebo+Pemetrexed+Platinum Agent
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5906
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.96

Secondary: Percentage of Participants with an Objective Response Assessed Using Response Evaluation Criteria in Solid Tumors (RECIST) Version (V) 1.1

End point title	Percentage of Participants with an Objective Response Assessed Using Response Evaluation Criteria in Solid Tumors (RECIST) Version (V) 1.1

End point description:

Objective response is defined as a complete response (CR) or partial response (PR). Participants without a post-baseline tumor assessment will be considered as nonresponders. CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Randomized participants with measurable disease at baseline were considered for analysis of this end point.

End point type	Secondary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until disease progression or death (up to approximately 20 months)

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	67	56	61
Units: percentage of participants				
number (confidence interval 95%)	51.5 (38.88 to 64.01)	44.8 (32.6 to 57.42)	28.6 (17.3 to 42.21)	36.1 (24.16 to 49.37)

Statistical analyses

Statistical analysis title	Statistical analysis I
Comparison groups	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent v Placebo+Bevacizumab+Paclitaxel+Platinum Agent
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4385
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rates
Point estimate	6.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.21
upper limit	23.68

Statistical analysis title	Statistical analysis II
Comparison groups	Onartuzumab+Pemetrexed+Platinum Agent v Placebo+Pemetrexed+Platinum Agent
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3892
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rates
Point estimate	-7.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.38
upper limit	9.39

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR is defined as the time from the first occurrence of a documented objective response to disease progression. CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until disease progression or death (up to approximately 20 months)

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[1]	0[2]	0[3]	0[4]
Units: months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[1] - Due to lack of efficacy, it was decided not to evaluate DoR.

[2] - Due to lack of efficacy, it was decided not to evaluate DoR.

[3] - Due to lack of efficacy, it was decided not to evaluate DoR.

[4] - Due to lack of efficacy, it was decided not to evaluate DoR.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate includes tumor responses of CR, PR and SD. CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study.

End point type	Secondary

End point timeframe:

Screening, every 6 weeks during the first 4 cycles of treatment, and every 9 weeks thereafter until disease progression or death (up to approximately 20 months)

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent	Placebo+Pemetrexed+Platinum Agent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	0[7]	0[8]
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[5] - Due to general lack of efficacy, disease control rate was not analysed.

[6] - Due to general lack of efficacy, disease control rate was not analysed.

[7] - Due to general lack of efficacy, disease control rate was not analysed.

[8] - Due to general lack of efficacy, disease control rate was not analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Serum Onartuzumab Concentration (Cmin) on Day 1 of Cycles 1 and 4

End point title	Pre-dose Serum Onartuzumab Concentration (Cmin) on Day 1 of Cycles 1 and 4[9]

End point description:

All randomized participants with measurable pharmacokinetic (PK) data were considered for analysis of this end point.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hour) on Day 1 of Cycles 1 and Cycle 4

Notes:

[9] - 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: PK end point is reported for only onartuzumab arms and not for placebo arms.

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	58		
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1	28.8 (± 11.9)	44.5 (± 62.9)		
Cycle 4	60 (± 70.6)	61.1 (± 37.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose Serum Onartuzumab Concentration (Cmax) on Day 1 of Cycles 1 and 4

End point title	Post-dose Serum Onartuzumab Concentration (Cmax) on Day 1 of Cycles 1 and 4[10]

End point description:

All randomized participants with measurable PK data were considered for analysis of this end point.

End point type	Secondary

End point timeframe:

30 minutes post-dose on Day 1 of Cycles 1 and 4

Notes:

[10] - 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: PK end point is reported for only onartuzumab arms and not for placebo arms.

End point values	Onartuzumab+ Bevacizumab+ Paclitaxel+Platinum Agent	Onartuzumab+ Pemetrexed+Platinum Agent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	58		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1	348 (± 361)	330 (± 112)		
Cycle 4	403 (± 139)	370 (± 141)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-therapeutic Antibodies (ATA) Against Onartuzumab

End point title	Number of Participants with Anti-therapeutic Antibodies (ATA) Against Onartuzumab

End point description:

Included all participants who received study treatment and had at least 1 postdose sample available for ATA analysis.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hour) on Day 1 of Cycles 1 and 4 and at study drug discontinuation visit (up to approximately 20 months)

End point values	Onartuzumab participants			
Subject group type	Subject analysis set			
Number of subjects analysed	109			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Up to 20 months

Adverse event reporting additional description:

Adverse events data were reported for safety population which included all participants who were randomized and received at least one dose of study treatment, with participants allocated to the treatment arm associated with the regimen actually received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 mg/kg IV infusion followed by bevacizumab 15 mg/kg IV followed by paclitaxel 200 mg/m^2 IV followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and bevacizumab 15 mg/kg IV on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Bevacizumab+Paclitaxel+Platinum Agent

Reporting group description:

Induction phase: participants received placebo IV infusion followed by bevacizumab 15 mg/kg IV followed by paclitaxel 200 mg/m^2 IV followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and bevacizumab 15 mg/kg IV on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Onartuzumab+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received onartuzumab 15 mg/kg IV infusion followed by pemetrexed 500 mg/m^2 IV followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received onartuzumab 15 mg/kg IV infusion and pemetrexed 500 mg/m^2 IV on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Reporting group title	Placebo+Pemetrexed+Platinum Agent

Reporting group description:

Induction phase: participants received placebo infusion followed by pemetrexed 500 mg/m^2 IV followed by carboplatin (AUC 6 IV) or cisplatin (75 mg/m^2 IV) on Day 1 of every cycle of 21 days for up to 4 cycles. Carboplatin or cisplatin platinum therapy was chosen as per investigator's discretion. Participants who experienced disease progression at any time during the induction phase discontinued all study treatment. In the absence of disease progression, after the 4-Cycle induction phase, participants began maintenance phase. Maintenance phase: participants received placebo infusion and pemetrexed 500 mg/m^2 IV on Day 1 of every cycle, until there was evidence of disease progression, death, or unacceptable toxicity, whichever occurred first.

Serious adverse events	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+Pemetrexed+Platinum Agent
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 69 (34.78%)	21 / 69 (30.43%)	17 / 58 (29.31%)
number of deaths (all causes)	3	4	0
number of deaths resulting from adverse events			
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Arterial occlusive disease			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Deep vein thrombosis			
subjects affected / exposed	3 / 69 (4.35%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Venous thrombosis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 69 (1.45%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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 physical health deterioration			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Impaired healing			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Cough			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
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			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Increased bronchial secretion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Pleural effusion			

subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
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	1 / 69 (1.45%)	2 / 69 (2.90%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 69 (0.00%)	2 / 69 (2.90%)	3 / 58 (5.17%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Investigations			
Weight decreased			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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			
Cardiac arrest			

subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 69 (0.00%)	3 / 69 (4.35%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 69 (1.45%)	1 / 69 (1.45%)	0 / 58 (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
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	5 / 69 (7.25%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	5 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 69 (0.00%)	2 / 69 (2.90%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Pancytopenia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spontaneous haematoma			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Thrombocytopenia			
subjects affected / exposed	1 / 69 (1.45%)	1 / 69 (1.45%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Diarrhoea			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Diverticular perforation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Dysphagia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Gastric ulcer			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loose tooth			

subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Nausea			
subjects affected / exposed	2 / 69 (2.90%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 69 (4.35%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Groin pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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

Intervertebral disc protrusion			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Peritonitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	4 / 69 (5.80%)	2 / 69 (2.90%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	1 / 4	1 / 2	1 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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	1 / 69 (1.45%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Urinary tract infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	0 / 58 (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
Urosepsis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Wound infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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	2 / 69 (2.90%)	2 / 69 (2.90%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	0 / 58 (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
Hyponatraemia			
subjects affected / exposed	2 / 69 (2.90%)	1 / 69 (1.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo+Pemetrexed+Platinum Agent		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 57 (38.60%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arterial occlusive disease			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypertension				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Impaired healing				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchitis chronic				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				

subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Increased bronchial secretion				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Guillain-Barre syndrome				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Neutropenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Spontaneous haematoma				

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo positional				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Loose tooth				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Onartuzumab+Bevacizumab+Paclitaxel+Platinum Agent	Placebo+Bevacizumab+Paclitaxel+Platinum Agent	Onartuzumab+Pemetrexed+Platinum Agent
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 69 (94.20%)	66 / 69 (95.65%)	57 / 58 (98.28%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 69 (4.35%)	0 / 69 (0.00%)	4 / 58 (6.90%)
occurrences (all)	3	0	5
Hypertension			
subjects affected / exposed	16 / 69 (23.19%)	20 / 69 (28.99%)	4 / 58 (6.90%)
occurrences (all)	19	29	4
Hypotension			
subjects affected / exposed	5 / 69 (7.25%)	4 / 69 (5.80%)	5 / 58 (8.62%)
occurrences (all)	5	4	6
Thrombosis			
subjects affected / exposed	4 / 69 (5.80%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 69 (15.94%)	8 / 69 (11.59%)	13 / 58 (22.41%)
occurrences (all)	12	9	18
Chest pain			
subjects affected / exposed	2 / 69 (2.90%)	7 / 69 (10.14%)	4 / 58 (6.90%)
occurrences (all)	2	7	4
Fatigue			
subjects affected / exposed	34 / 69 (49.28%)	25 / 69 (36.23%)	21 / 58 (36.21%)
occurrences (all)	40	34	36
Mucosal inflammation			
subjects affected / exposed	2 / 69 (2.90%)	7 / 69 (10.14%)	4 / 58 (6.90%)
occurrences (all)	3	8	4
Oedema peripheral			
subjects affected / exposed	23 / 69 (33.33%)	2 / 69 (2.90%)	30 / 58 (51.72%)
occurrences (all)	32	2	40
Pain			

subjects affected / exposed	5 / 69 (7.25%)	5 / 69 (7.25%)	6 / 58 (10.34%)
occurrences (all)	6	6	8
Pyrexia			
subjects affected / exposed	4 / 69 (5.80%)	3 / 69 (4.35%)	1 / 58 (1.72%)
occurrences (all)	7	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 69 (27.54%)	12 / 69 (17.39%)	8 / 58 (13.79%)
occurrences (all)	24	15	9
Dysphonia			
subjects affected / exposed	6 / 69 (8.70%)	3 / 69 (4.35%)	1 / 58 (1.72%)
occurrences (all)	6	3	1
Dyspnoea			
subjects affected / exposed	18 / 69 (26.09%)	16 / 69 (23.19%)	13 / 58 (22.41%)
occurrences (all)	18	18	13
Epistaxis			
subjects affected / exposed	13 / 69 (18.84%)	8 / 69 (11.59%)	1 / 58 (1.72%)
occurrences (all)	13	10	1
Oropharyngeal pain			
subjects affected / exposed	5 / 69 (7.25%)	2 / 69 (2.90%)	3 / 58 (5.17%)
occurrences (all)	5	2	5
Pulmonary embolism			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 69 (2.90%)	2 / 69 (2.90%)	4 / 58 (6.90%)
occurrences (all)	2	2	5
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 69 (5.80%)	2 / 69 (2.90%)	6 / 58 (10.34%)
occurrences (all)	4	2	6
Depression			
subjects affected / exposed	6 / 69 (8.70%)	1 / 69 (1.45%)	4 / 58 (6.90%)
occurrences (all)	6	1	4
Insomnia			

subjects affected / exposed	5 / 69 (7.25%)	10 / 69 (14.49%)	14 / 58 (24.14%)
occurrences (all)	5	15	15
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 69 (2.90%)	2 / 69 (2.90%)	3 / 58 (5.17%)
occurrences (all)	2	4	3
Blood creatinine increased			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Neutrophil count decreased			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	4
Weight decreased			
subjects affected / exposed	4 / 69 (5.80%)	4 / 69 (5.80%)	4 / 58 (6.90%)
occurrences (all)	4	4	5
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 69 (0.00%)	4 / 69 (5.80%)	0 / 58 (0.00%)
occurrences (all)	0	4	0
Procedural pain			
subjects affected / exposed	2 / 69 (2.90%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	3
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 69 (5.80%)	2 / 69 (2.90%)	3 / 58 (5.17%)
occurrences (all)	4	2	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 69 (7.25%)	6 / 69 (8.70%)	5 / 58 (8.62%)
occurrences (all)	5	6	5
Dysgeusia			
subjects affected / exposed	3 / 69 (4.35%)	5 / 69 (7.25%)	6 / 58 (10.34%)
occurrences (all)	3	5	8
Headache			
subjects affected / exposed	10 / 69 (14.49%)	6 / 69 (8.70%)	7 / 58 (12.07%)
occurrences (all)	11	6	7

Neuropathy peripheral			
subjects affected / exposed	22 / 69 (31.88%)	15 / 69 (21.74%)	2 / 58 (3.45%)
occurrences (all)	25	21	2
Paraesthesia			
subjects affected / exposed	7 / 69 (10.14%)	3 / 69 (4.35%)	1 / 58 (1.72%)
occurrences (all)	8	3	2
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 69 (8.70%)	7 / 69 (10.14%)	1 / 58 (1.72%)
occurrences (all)	6	9	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 69 (21.74%)	19 / 69 (27.54%)	24 / 58 (41.38%)
occurrences (all)	21	23	32
Leukopenia			
subjects affected / exposed	1 / 69 (1.45%)	4 / 69 (5.80%)	2 / 58 (3.45%)
occurrences (all)	1	4	2
Neutropenia			
subjects affected / exposed	19 / 69 (27.54%)	12 / 69 (17.39%)	11 / 58 (18.97%)
occurrences (all)	31	18	16
Thrombocytopenia			
subjects affected / exposed	13 / 69 (18.84%)	11 / 69 (15.94%)	12 / 58 (20.69%)
occurrences (all)	22	15	16
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Tinnitus			
subjects affected / exposed	0 / 69 (0.00%)	2 / 69 (2.90%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Lacrimation increased			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Periorbital oedema			

subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4
Vision blurred			
subjects affected / exposed	4 / 69 (5.80%)	1 / 69 (1.45%)	2 / 58 (3.45%)
occurrences (all)	4	1	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 69 (4.35%)	3 / 69 (4.35%)	4 / 58 (6.90%)
occurrences (all)	3	3	5
Abdominal pain upper			
subjects affected / exposed	2 / 69 (2.90%)	2 / 69 (2.90%)	2 / 58 (3.45%)
occurrences (all)	3	3	2
Constipation			
subjects affected / exposed	24 / 69 (34.78%)	15 / 69 (21.74%)	23 / 58 (39.66%)
occurrences (all)	28	18	26
Diarrhoea			
subjects affected / exposed	13 / 69 (18.84%)	19 / 69 (27.54%)	16 / 58 (27.59%)
occurrences (all)	18	25	19
Dyspepsia			
subjects affected / exposed	7 / 69 (10.14%)	4 / 69 (5.80%)	4 / 58 (6.90%)
occurrences (all)	7	5	4
Nausea			
subjects affected / exposed	28 / 69 (40.58%)	24 / 69 (34.78%)	28 / 58 (48.28%)
occurrences (all)	40	33	52
Stomatitis			
subjects affected / exposed	3 / 69 (4.35%)	5 / 69 (7.25%)	6 / 58 (10.34%)
occurrences (all)	3	5	6
Vomiting			
subjects affected / exposed	13 / 69 (18.84%)	16 / 69 (23.19%)	16 / 58 (27.59%)
occurrences (all)	19	18	19
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 69 (52.17%)	32 / 69 (46.38%)	4 / 58 (6.90%)
occurrences (all)	36	32	4
Dry skin			

subjects affected / exposed	2 / 69 (2.90%)	4 / 69 (5.80%)	4 / 58 (6.90%)
occurrences (all)	2	7	4
Pruritus			
subjects affected / exposed	2 / 69 (2.90%)	3 / 69 (4.35%)	3 / 58 (5.17%)
occurrences (all)	3	5	3
Rash			
subjects affected / exposed	4 / 69 (5.80%)	5 / 69 (7.25%)	5 / 58 (8.62%)
occurrences (all)	4	5	5
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 69 (5.80%)	2 / 69 (2.90%)	1 / 58 (1.72%)
occurrences (all)	4	2	1
Proteinuria			
subjects affected / exposed	8 / 69 (11.59%)	8 / 69 (11.59%)	0 / 58 (0.00%)
occurrences (all)	9	15	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 69 (14.49%)	7 / 69 (10.14%)	5 / 58 (8.62%)
occurrences (all)	13	9	6
Back pain			
subjects affected / exposed	8 / 69 (11.59%)	10 / 69 (14.49%)	11 / 58 (18.97%)
occurrences (all)	9	11	11
Bone pain			
subjects affected / exposed	2 / 69 (2.90%)	3 / 69 (4.35%)	3 / 58 (5.17%)
occurrences (all)	4	6	3
Muscular weakness			
subjects affected / exposed	2 / 69 (2.90%)	3 / 69 (4.35%)	0 / 58 (0.00%)
occurrences (all)	2	3	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 69 (1.45%)	3 / 69 (4.35%)	3 / 58 (5.17%)
occurrences (all)	1	3	4
Musculoskeletal pain			
subjects affected / exposed	4 / 69 (5.80%)	6 / 69 (8.70%)	6 / 58 (10.34%)
occurrences (all)	4	6	8
Myalgia			

subjects affected / exposed	13 / 69 (18.84%)	13 / 69 (18.84%)	1 / 58 (1.72%)
occurrences (all)	25	23	1
Pain in extremity			
subjects affected / exposed	7 / 69 (10.14%)	6 / 69 (8.70%)	8 / 58 (13.79%)
occurrences (all)	7	9	8
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 69 (1.45%)	4 / 69 (5.80%)	2 / 58 (3.45%)
occurrences (all)	1	4	2
Conjunctivitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Folliculitis			
subjects affected / exposed	4 / 69 (5.80%)	0 / 69 (0.00%)	0 / 58 (0.00%)
occurrences (all)	4	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 69 (2.90%)	2 / 69 (2.90%)	2 / 58 (3.45%)
occurrences (all)	2	2	2
Oral candidiasis			
subjects affected / exposed	2 / 69 (2.90%)	2 / 69 (2.90%)	2 / 58 (3.45%)
occurrences (all)	3	2	2
Pneumonia			
subjects affected / exposed	3 / 69 (4.35%)	4 / 69 (5.80%)	7 / 58 (12.07%)
occurrences (all)	3	4	7
Upper respiratory tract infection			
subjects affected / exposed	3 / 69 (4.35%)	4 / 69 (5.80%)	2 / 58 (3.45%)
occurrences (all)	3	5	2
Urinary tract infection			
subjects affected / exposed	3 / 69 (4.35%)	7 / 69 (10.14%)	3 / 58 (5.17%)
occurrences (all)	4	7	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 69 (27.54%)	17 / 69 (24.64%)	19 / 58 (32.76%)
occurrences (all)	19	18	23
Dehydration			

subjects affected / exposed	6 / 69 (8.70%)	5 / 69 (7.25%)	8 / 58 (13.79%)
occurrences (all)	8	7	9
Hyperglycaemia			
subjects affected / exposed	4 / 69 (5.80%)	3 / 69 (4.35%)	8 / 58 (13.79%)
occurrences (all)	5	3	8
Hypoalbuminaemia			
subjects affected / exposed	10 / 69 (14.49%)	2 / 69 (2.90%)	12 / 58 (20.69%)
occurrences (all)	11	2	14
Hypocalcaemia			
subjects affected / exposed	7 / 69 (10.14%)	2 / 69 (2.90%)	6 / 58 (10.34%)
occurrences (all)	8	2	7
Hypokalaemia			
subjects affected / exposed	5 / 69 (7.25%)	2 / 69 (2.90%)	9 / 58 (15.52%)
occurrences (all)	6	3	11
Hypomagnesaemia			
subjects affected / exposed	5 / 69 (7.25%)	7 / 69 (10.14%)	9 / 58 (15.52%)
occurrences (all)	7	7	12
Hyponatraemia			
subjects affected / exposed	6 / 69 (8.70%)	2 / 69 (2.90%)	7 / 58 (12.07%)
occurrences (all)	10	2	9
Hypophosphataemia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	4

Non-serious adverse events	Placebo+Pemetrexed+Platinum Agent		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hypotension			

subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Thrombosis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	16		
Chest pain			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	23 / 57 (40.35%)		
occurrences (all)	27		
Mucosal inflammation			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	13		
Dysphonia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	2		
Dyspnoea			

subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	14		
Epistaxis			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	10		
Depression			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Weight decreased			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Neuropathy peripheral			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	39		

Leukopenia subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	15 / 57 (26.32%) 33		
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 57 (14.04%) 14		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4		
Tinnitus subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Lacrimation increased subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 6		
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Vision blurred subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		
Constipation			

subjects affected / exposed	24 / 57 (42.11%)		
occurrences (all)	29		
Diarrhoea			
subjects affected / exposed	13 / 57 (22.81%)		
occurrences (all)	15		
Dyspepsia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	30 / 57 (52.63%)		
occurrences (all)	55		
Stomatitis			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	17 / 57 (29.82%)		
occurrences (all)	22		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	14		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Proteinuria			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	8		
Bone pain			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	8		
Muscular weakness			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	10		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Folliculitis			

subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Oral candidiasis			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	12		
Dehydration			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	25		
Hyperglycaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	13		

Hypomagnesaemia subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	The infusion time for onartuzumab/placebo and carboplatin was clarified. The subset of participants who consent to additional blood draws for pharmacokinetic (PK) analysis might be subjected to safety issues with a shorter than standard infusion time for the given chemotherapeutic agents, thus, the protocol was amended to indicate that all participants were to be dosed on the same schedule. With regard to carboplatin dose calculation, the correction for the Cockcroft-Gault method for calculation of creatinine clearance in females, which was inadvertently omitted from the original protocol, was provided. For the participants who consent to additional PK sampling, in an effort to shorten their time in the clinic, the final sampling timepoint for plasma paclitaxel pharmacokinetics at Cycle 1 Day 1 and Cycle 4 Day 1 was changed from 8 hours to 6 hours after the end of the paclitaxel infusion for participants in Cohort 1.
13 April 2012	The study inclusion criterion regarding participants who undergo prior adjuvant therapy was clarified to include chemoradiotherapy along with chemotherapy. In the study inclusion criteria regarding contraception, for Cohort 1, the required duration of the use of adequate contraception after study treatment was increased in accordance with the current labeling for paclitaxel. The study exclusion criterion regarding participants with endothelial growth factor receptor (EGFR)-activating mutations who were suitable for anti-EGFR therapy was modified to allow for cases where treatment was unavailable to or refused by the participant. The exclusion criterion regarding history of malignancy was modified to allow for in-situ cancer or localized prostate cancer that was treated surgically with curative intent. Clarification was provided regarding the administration of chemotherapy in accordance with local standard of care. Clarification was provided regarding the use of positron emission tomography (PET) - Computed tomography (CT) for tumor and response evaluations. With regard to tumor tissue samples, clarification was provided on the number of tissue slides to be submitted when EGFR status was already known. It was clarified that baseline weight (rather than screening weight) will be used to calculate onartuzumab/placebo dosage. For Cohort 1, the timing for paclitaxel administration was clarified to be after bevacizumab infusion, not after onartuzumab/placebo. For Cohorts 1 and 2, the timing of carboplatin treatment after paclitaxel or pemetrexed infusion has been clarified. The maximum allowed onartuzumab/placebo dose delay was extended from 7 days to one treatment cycle. To more fully comply with updated regulations, serious adverse events (SAEs) and pregnancies were planned to be reported within 24 hours rather than 1 working day.
03 April 2013	For the Sponsor's internal decision-making process, a third data review by the Internal Monitoring Committee (IMC) was added to assess the treatment effect in participants with MET diagnostic-positive tumors at an earlier time point than the planned final analysis. For consistency with other clinical studies with onartuzumab, the observation period following onartuzumab/placebo infusion was reduced to greater than or equal to (≥) 30 minutes after the second and subsequent doses. It has been clarified that if a chemotherapy regimen other than those specified in the protocol was administered, onartuzumab will be discontinued. Clarification was provided regarding what tests were required to be performed as part of an evaluation for proteinuria. The measurement of partial thromboplastin time (PTT), which was inadvertently included in the original protocol, was removed from the exclusion criterion regarding coagulation testing at screening. It was clarified that EGFR testing was not required to be completed prior to randomization.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 October 2013	A decision was made by the sponsor to discontinue further clinical development of onartuzumab.	-

Notes:

Limitations and caveats

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

The clinical development of onartuzumab was terminated as per decision made by sponsor primarily due to limited efficacy observed in the conduct of this study and was not based on safety-related issues.

Notes: