Clinical trial results:
A Randomized, Phase II, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Onartuzumab and/or Bevacizumab in Combination with Paclitaxel in Patients with Metastatic, Triple-Negative Breast Cancer

Summary

EudraCT number	2010-020101-32
Trial protocol	ES FR BE DE GB
Global end of trial date	18 April 2016

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	06 July 2016

Trial information

Trial identification

Sponsor protocol code	GO01334

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01186991
WHO universal trial number (UTN)	-
Other trial identifiers	OAM4861g: Alternate sponsor trial identifier

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland,
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 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	18 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2016
Global end of trial reached?	Yes
Global end of trial date	18 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the clinical benefit of onartuzumab+ bevacizumab + paclitaxel (Onar+Bev+Pac) and onartuzumab+ placebo + paclitaxel (Onar+Pbo+Pac) relative to placebo + bevacizumab + paclitaxel (Pbo+Bev+Pac), as measured by investigator assessed Progression Free Survival (PFS), in patients with metastatic or locally recurrent, Triple-Negative Breast Cancer (TNBC) who have received no prior systemic therapy or have progressed following first-line therapy for metastatic disease.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2011
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	United States: 69
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	185
EEA total number of subjects	116

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)	153
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 51 centers in 6 countries.

Pre-assignment

Screening details:

A total of 250 participants were screened for entry into the study; there were 65 screen failures. A total of 185 participants were randomized in a 1:1:1 ratio to three treatment arms.

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 + Placebo + Paclitaxel

Arm description:

Onartuzumab was administered every 2 weeks, on Day 1 and 15 of each 28 day cycle. Paclitaxel was administered on Day 1, 8 and 15 of each 28 day cycle. Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle.

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

Dosage and administration details:

Placebo dosage consisted of 250 cc of 0.9% NSS (saline IV solution, 0.9%). The initial dose of onartuzumab/placebo was delivered over 90 ±15 minutes. If the first infusion was tolerated without infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ±10 minutes.

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

Dosage and administration details:

10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. The dose of onartuzumab was based on the patient’s weight at screening and remained the same throughout the study. The initial dose of onartuzumab/placebo was delivered over 90 ±15 minutes. If the first
infusion was tolerated without infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ±10 minutes.

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

Dosage and administration details:

Administered at dose of 90 mg/m2 on Day 1, 8, and 15 of each 28 day cycle. Administered over a

period of approximately 1 hour. Due to the known potential for allergic reactions to paclitaxel, participants were pre-medicated with dexamethasone, diphenhydramine, and an H2 blocker 30−60 minutes prior to the paclitaxel administration.

Arm title	Onartuzumab + Bevacizumab + Paclitaxel

Arm description:

Onartuzumab, alone or in combination with Bevacizumab, was administered every two weeks, on Day 1 and 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.

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

Dosage and administration details:

10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. The dose of onartuzumab was based on the patient’s weight at screening and remained the same throughout the study. The initial dose of onartuzumab/placebo was delivered over 90 ±15 minutes. If the first
infusion was tolerated without infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ±10 minutes.

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

Dosage and administration details:

Administered at dose of 90 mg/m2 on Day 1, 8, and 15 of each 28 day cycle. Administered over a period of approximately 1 hour. Due to the known potential for allergic reactions to paclitaxel, participants were pre-medicated with dexamethasone, diphenhydramine, and an H2 blocker 30−60 minutes prior to the paclitaxel administration.

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

Dosage and administration details:

Administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. The dose of bevacizumab was based on the participant's weight at screening and remained the same throughout the study. The initial dose of bevacizumab/placebo was delivered over 90 ±15 minutes. If the first infusion was tolerated without any infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ± 10 minutes.

Arm title	Placebo + Bevacizumab + Paclitaxel

Arm description:

Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.

Arm type	Active comparator

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

Dosage and administration details:

Placebo dosage consisted of 250 cc of 0.9% NSS (saline IV solution, 0.9%). The initial dose of bevacizumab/placebo was delivered over 90 ±15 minutes. If the first infusion was tolerated without any infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ± 10 minutes.

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

Dosage and administration details:

Administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. The dose of bevacizumab was based on the participant's weight at screening and remained the same throughout the study. The initial dose of bevacizumab/placebo was delivered over 90 ±15 minutes. If the first infusion was tolerated without any infusion-associated AEs (fever and/or chills), the second infusion was delivered over 60 ± 10 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over 30 ± 10 minutes.

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

Dosage and administration details:

Administered at dose of 90 mg/m2 on Day 1, 8, and 15 of each 28 day cycle. Administered over a period of approximately 1 hour. Due to the known potential for allergic reactions to paclitaxel, participants were pre-medicated with dexamethasone, diphenhydramine, and an H2 blocker 30−60 minutes prior to the paclitaxel administration.

Number of subjects in period 1	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel
Started	60	63	62
Completed	0	0	0
Not completed	60	63	62
Physician decision	-	-	2
Adverse event, non-fatal	-	-	1
Death	44	45	42
Study terminated by sponsor	13	15	16
Lost to follow-up	-	-	1
Withdrawal by subject	3	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Onartuzumab + Placebo + Paclitaxel
Reporting group description:	
Onartuzumab was administered every 2 weeks, on Day 1 and 15 of each 28 day cycle. Paclitaxel was administered on Day 1, 8 and 15 of each 28 day cycle. Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle.	
Reporting group title	Onartuzumab + Bevacizumab + Paclitaxel
Reporting group description:	
Onartuzumab, alone or in combination with Bevacizumab, was administered every two weeks, on Day 1 and 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.	
Reporting group title	Placebo + Bevacizumab + Paclitaxel
Reporting group description:	
Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.	

Reporting group values	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel
Number of subjects	60	63	62
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.4 ± 12.5	 53.5 ± 11.7	 52.8 ± 9.1
Gender categorical Units: Subjects			
Female	60	63	62
Male	0	0	0

Reporting group values	Total		
Number of subjects	185		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	185		
Male	0		

End points

End points reporting groups

Reporting group title	Onartuzumab + Placebo + Paclitaxel
Reporting group description:	
Onartuzumab was administered every 2 weeks, on Day 1 and 15 of each 28 day cycle. Paclitaxel was administered on Day 1, 8 and 15 of each 28 day cycle. Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle.	
Reporting group title	Onartuzumab + Bevacizumab + Paclitaxel
Reporting group description:	
Onartuzumab, alone or in combination with Bevacizumab, was administered every two weeks, on Day 1 and 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.	
Reporting group title	Placebo + Bevacizumab + Paclitaxel
Reporting group description:	
Placebo was administered by IV infusion every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, on Day 1 and Day 15 of each 28-day cycle. Paclitaxel was administered on Day 1, 8, and 15 of each 28-day cycle.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
Analyzed population was randomized participants.	
End point type	Primary
End point timeframe:	
Time from randomization to disease progression or relapse (assessed using Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1) or death from any cause (defined as death within 30 days of last study treatment), whichever occurs first.	

End point values	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	63	62	
Units: Months				
median (full range (min-max))	5.4 (0 to 17.3)	7.3 (0 to 16.6)	7.2 (1.6 to 23)	

Statistical analyses

Statistical analysis title	PFS Met+Pbo+Pac relative to Pbo+Bev+Pac
Comparison groups	Onartuzumab + Placebo + Paclitaxel v Placebo + Bevacizumab + Paclitaxel

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.739
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	2.675

Statistical analysis title	PFS Met+Bev+Pac relative to Pbo+Bev+Pac
Comparison groups	Onartuzumab + Bevacizumab + Paclitaxel v Placebo + Bevacizumab + Paclitaxel
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.689
upper limit	1.702

Secondary: Objective Response (OR)	
End point title	Objective Response (OR)
End point description:	
Analyzed population was randomized participants with measurable disease at baseline.	
End point type	Secondary
End point timeframe:	
Complete or partial response maintained >/= 4 weeks	

End point values	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	19	29	
Units: Percentage				
number (confidence interval 95%)	27.5 (15.9 to 40.6)	42.2 (28.6 to 57.1)	54.7 (41 to 68.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response

End point title	Duration of Objective Response

End point description:

Analyzed population was randomized participants with measurable disease at baseline

End point type	Secondary

End point timeframe:

Initial complete or partial response to disease progression or death on study from any cause, whichever occurs first.

End point values	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	19	29	
Units: Months				
median (confidence interval 95%)	5.8 (3.71 to 99999)	9.8 (4.67 to 99999)	7.5 (5.36 to 11.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is the time from randomization to death from any cause; data reflects randomized population

End point type	Secondary

End point timeframe:

Through the end of the study

End point values	Onartuzumab + Placebo + Paclitaxel	Onartuzumab + Bevacizumab + Paclitaxel	Placebo + Bevacizumab + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	63	62	
Units: Months				
median (confidence interval 95%)	13.4 (9.76 to 9999)	14.7 (10.58 to 9999)	17.4 (12.55 to 9999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time frame for the safety data was throughout the course of the study until the data cutoff date.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	n/a

Reporting groups

Reporting group title	Onartuzumab +Bevacizumab +Paclitaxel
Reporting group description: -	
Reporting group title	Onartuzumab + Placebo + Paclitaxel
Reporting group description: -	
Reporting group title	Placebo + Bevacizumab +Paclitaxel
Reporting group description: -	

Serious adverse events	Onartuzumab +Bevacizumab +Paclitaxel	Onartuzumab + Placebo + Paclitaxel	Placebo + Bevacizumab +Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 62 (35.48%)	13 / 58 (22.41%)	15 / 62 (24.19%)
number of deaths (all causes)	45	44	42
number of deaths resulting from adverse events	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemorrhagic tumour necrosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Aortic thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Venous thrombosis limb			

subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Hypertension			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Medical device complication			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Pyrexia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Asthenia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			

subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 62 (4.84%)	1 / 58 (1.72%)	4 / 62 (6.45%)
occurrences causally related to treatment / all	3 / 3	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Pulmonary haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 62 (4.84%)	2 / 58 (3.45%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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

Pleural effusion			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hallucination			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Confusional state			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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			
Ejection fraction decreased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Heart rate irregular			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Staphylococcus test positive			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dural arteriovenous fistula			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Hypokinesia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory loss			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Pancytopenia			

subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Gastrointestinal perforation			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Neutropenic colitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Diarrhoea			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Intestinal obstruction			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Oesophagitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 62 (0.00%)	2 / 58 (3.45%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Hepatic failure			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infarction			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 62 (3.23%)	0 / 58 (0.00%)	0 / 62 (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
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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

Periarthritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 62 (3.23%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Cellulitis			
subjects affected / exposed	2 / 62 (3.23%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Device related infection			

subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	0 / 62 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	0 / 62 (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
Dehydration			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Onartuzumab +Bevacizumab +Paclitaxel	Onartuzumab + Placebo + Paclitaxel	Placebo + Bevacizumab +Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 62 (98.39%)	57 / 58 (98.28%)	61 / 62 (98.39%)
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 62 (3.23%)	1 / 58 (1.72%)	5 / 62 (8.06%)
occurrences (all)	3	1	5
Hot flush			
subjects affected / exposed	4 / 62 (6.45%)	6 / 58 (10.34%)	7 / 62 (11.29%)
occurrences (all)	4	7	8
Phlebitis			
subjects affected / exposed	5 / 62 (8.06%)	2 / 58 (3.45%)	0 / 62 (0.00%)
occurrences (all)	5	2	0
Lymphoedema			
subjects affected / exposed	7 / 62 (11.29%)	8 / 58 (13.79%)	5 / 62 (8.06%)
occurrences (all)	7	8	6
Hypotension			
subjects affected / exposed	2 / 62 (3.23%)	3 / 58 (5.17%)	0 / 62 (0.00%)
occurrences (all)	3	3	0
Hypertension			
subjects affected / exposed	13 / 62 (20.97%)	3 / 58 (5.17%)	25 / 62 (40.32%)
occurrences (all)	13	3	32
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 62 (8.06%)	7 / 58 (12.07%)	4 / 62 (6.45%)
occurrences (all)	5	10	4
Asthenia			
subjects affected / exposed	17 / 62 (27.42%)	20 / 58 (34.48%)	19 / 62 (30.65%)
occurrences (all)	56	45	49
Mucosal inflammation			
subjects affected / exposed	10 / 62 (16.13%)	1 / 58 (1.72%)	11 / 62 (17.74%)
occurrences (all)	17	1	14
Generalised oedema			

subjects affected / exposed	2 / 62 (3.23%)	3 / 58 (5.17%)	0 / 62 (0.00%)
occurrences (all)	2	6	0
Chills			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	2	3	5
Face oedema			
subjects affected / exposed	6 / 62 (9.68%)	8 / 58 (13.79%)	0 / 62 (0.00%)
occurrences (all)	11	9	0
Fatigue			
subjects affected / exposed	29 / 62 (46.77%)	24 / 58 (41.38%)	32 / 62 (51.61%)
occurrences (all)	40	35	41
Pyrexia			
subjects affected / exposed	2 / 62 (3.23%)	8 / 58 (13.79%)	11 / 62 (17.74%)
occurrences (all)	5	11	14
Peripheral swelling			
subjects affected / exposed	5 / 62 (8.06%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences (all)	11	0	2
Oedema peripheral			
subjects affected / exposed	33 / 62 (53.23%)	34 / 58 (58.62%)	10 / 62 (16.13%)
occurrences (all)	69	77	10
Pain			
subjects affected / exposed	3 / 62 (4.84%)	3 / 58 (5.17%)	2 / 62 (3.23%)
occurrences (all)	3	4	2
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 62 (1.61%)	5 / 58 (8.62%)	2 / 62 (3.23%)
occurrences (all)	4	5	2
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	8 / 62 (12.90%)	2 / 58 (3.45%)	7 / 62 (11.29%)
occurrences (all)	9	2	8
Cough			
subjects affected / exposed	14 / 62 (22.58%)	9 / 58 (15.52%)	15 / 62 (24.19%)
occurrences (all)	19	10	19
Oropharyngeal pain			

subjects affected / exposed	6 / 62 (9.68%)	4 / 58 (6.90%)	10 / 62 (16.13%)
occurrences (all)	9	4	11
Dyspnoea			
subjects affected / exposed	12 / 62 (19.35%)	13 / 58 (22.41%)	11 / 62 (17.74%)
occurrences (all)	15	17	13
Rhinitis allergic			
subjects affected / exposed	4 / 62 (6.45%)	0 / 58 (0.00%)	0 / 62 (0.00%)
occurrences (all)	4	0	0
Rhinorrhoea			
subjects affected / exposed	7 / 62 (11.29%)	2 / 58 (3.45%)	3 / 62 (4.84%)
occurrences (all)	7	2	3
Epistaxis			
subjects affected / exposed	31 / 62 (50.00%)	9 / 58 (15.52%)	37 / 62 (59.68%)
occurrences (all)	49	12	57
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 62 (8.06%)	4 / 58 (6.90%)	4 / 62 (6.45%)
occurrences (all)	5	5	4
Anxiety			
subjects affected / exposed	5 / 62 (8.06%)	6 / 58 (10.34%)	5 / 62 (8.06%)
occurrences (all)	5	9	5
Insomnia			
subjects affected / exposed	13 / 62 (20.97%)	7 / 58 (12.07%)	12 / 62 (19.35%)
occurrences (all)	14	7	13
Investigations			
White blood cell count decreased			
subjects affected / exposed	5 / 62 (8.06%)	1 / 58 (1.72%)	1 / 62 (1.61%)
occurrences (all)	13	1	5
Alanine aminotransferase increased			
subjects affected / exposed	2 / 62 (3.23%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	3	4	1
Neutrophil count decreased			
subjects affected / exposed	5 / 62 (8.06%)	3 / 58 (5.17%)	5 / 62 (8.06%)
occurrences (all)	11	4	8
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	1	6	1
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 62 (27.42%)	9 / 58 (15.52%)	18 / 62 (29.03%)
occurrences (all)	24	10	27
Dizziness			
subjects affected / exposed	6 / 62 (9.68%)	5 / 58 (8.62%)	8 / 62 (12.90%)
occurrences (all)	7	5	9
Dysaesthesia			
subjects affected / exposed	2 / 62 (3.23%)	1 / 58 (1.72%)	4 / 62 (6.45%)
occurrences (all)	4	2	6
Dysgeusia			
subjects affected / exposed	7 / 62 (11.29%)	7 / 58 (12.07%)	9 / 62 (14.52%)
occurrences (all)	9	7	9
Paraesthesia			
subjects affected / exposed	16 / 62 (25.81%)	8 / 58 (13.79%)	21 / 62 (33.87%)
occurrences (all)	24	11	29
Neuropathy peripheral			
subjects affected / exposed	18 / 62 (29.03%)	15 / 58 (25.86%)	21 / 62 (33.87%)
occurrences (all)	27	33	25
Hypoaesthesia			
subjects affected / exposed	3 / 62 (4.84%)	4 / 58 (6.90%)	5 / 62 (8.06%)
occurrences (all)	4	4	6
Lethargy			
subjects affected / exposed	2 / 62 (3.23%)	2 / 58 (3.45%)	4 / 62 (6.45%)
occurrences (all)	3	3	5
Neuralgia			
subjects affected / exposed	0 / 62 (0.00%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	0	4	1
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 62 (16.13%)	10 / 58 (17.24%)	5 / 62 (8.06%)
occurrences (all)	11	12	7
Sciatica			

subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	4 / 62 (6.45%)
occurrences (all)	1	0	4
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 62 (6.45%)	0 / 58 (0.00%)	3 / 62 (4.84%)
occurrences (all)	5	0	3
Anaemia			
subjects affected / exposed	13 / 62 (20.97%)	2 / 58 (3.45%)	10 / 62 (16.13%)
occurrences (all)	22	2	13
Neutropenia			
subjects affected / exposed	16 / 62 (25.81%)	10 / 58 (17.24%)	11 / 62 (17.74%)
occurrences (all)	41	19	21
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	3 / 62 (4.84%)
occurrences (all)	1	6	7
Tinnitus			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	1	3	1
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	5 / 62 (8.06%)
occurrences (all)	3	0	5
Lacrimation increased			
subjects affected / exposed	7 / 62 (11.29%)	1 / 58 (1.72%)	3 / 62 (4.84%)
occurrences (all)	9	1	3
Vision blurred			
subjects affected / exposed	1 / 62 (1.61%)	2 / 58 (3.45%)	4 / 62 (6.45%)
occurrences (all)	1	2	4
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	21 / 62 (33.87%)	16 / 58 (27.59%)	23 / 62 (37.10%)
occurrences (all)	26	18	30
Abdominal pain upper			
subjects affected / exposed	4 / 62 (6.45%)	5 / 58 (8.62%)	3 / 62 (4.84%)
occurrences (all)	5	6	3
Abdominal pain			

subjects affected / exposed	10 / 62 (16.13%)	13 / 58 (22.41%)	8 / 62 (12.90%)
occurrences (all)	13	17	12
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 62 (1.61%)	4 / 58 (6.90%)	5 / 62 (8.06%)
occurrences (all)	2	8	9
Diarrhoea			
subjects affected / exposed	33 / 62 (53.23%)	14 / 58 (24.14%)	32 / 62 (51.61%)
occurrences (all)	54	27	55
Dry mouth			
subjects affected / exposed	4 / 62 (6.45%)	4 / 58 (6.90%)	1 / 62 (1.61%)
occurrences (all)	4	6	1
Dyspepsia			
subjects affected / exposed	9 / 62 (14.52%)	4 / 58 (6.90%)	5 / 62 (8.06%)
occurrences (all)	11	5	5
Rectal haemorrhage			
subjects affected / exposed	4 / 62 (6.45%)	0 / 58 (0.00%)	2 / 62 (3.23%)
occurrences (all)	4	0	3
Haemorrhoids			
subjects affected / exposed	7 / 62 (11.29%)	4 / 58 (6.90%)	9 / 62 (14.52%)
occurrences (all)	8	5	15
Nausea			
subjects affected / exposed	24 / 62 (38.71%)	22 / 58 (37.93%)	26 / 62 (41.94%)
occurrences (all)	34	32	40
Oral pain			
subjects affected / exposed	4 / 62 (6.45%)	0 / 58 (0.00%)	1 / 62 (1.61%)
occurrences (all)	5	0	1
Stomatitis			
subjects affected / exposed	15 / 62 (24.19%)	3 / 58 (5.17%)	13 / 62 (20.97%)
occurrences (all)	22	3	17
Toothache			
subjects affected / exposed	2 / 62 (3.23%)	1 / 58 (1.72%)	5 / 62 (8.06%)
occurrences (all)	2	1	5
Vomiting			
subjects affected / exposed	10 / 62 (16.13%)	12 / 58 (20.69%)	13 / 62 (20.97%)
occurrences (all)	16	21	21
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	5 / 62 (8.06%)	5 / 58 (8.62%)	6 / 62 (9.68%)
occurrences (all)	6	8	6
Dry skin			
subjects affected / exposed	9 / 62 (14.52%)	7 / 58 (12.07%)	8 / 62 (12.90%)
occurrences (all)	9	9	8
Dermatitis acneiform			
subjects affected / exposed	5 / 62 (8.06%)	8 / 58 (13.79%)	5 / 62 (8.06%)
occurrences (all)	6	14	8
Alopecia			
subjects affected / exposed	30 / 62 (48.39%)	30 / 58 (51.72%)	38 / 62 (61.29%)
occurrences (all)	38	33	44
Acne			
subjects affected / exposed	5 / 62 (8.06%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	8	4	1
Nail discolouration			
subjects affected / exposed	5 / 62 (8.06%)	2 / 58 (3.45%)	9 / 62 (14.52%)
occurrences (all)	5	2	9
Nail disorder			
subjects affected / exposed	11 / 62 (17.74%)	4 / 58 (6.90%)	10 / 62 (16.13%)
occurrences (all)	21	6	11
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 62 (8.06%)	1 / 58 (1.72%)	1 / 62 (1.61%)
occurrences (all)	7	1	1
Nail toxicity			
subjects affected / exposed	5 / 62 (8.06%)	4 / 58 (6.90%)	4 / 62 (6.45%)
occurrences (all)	8	6	6
Rash erythematous			
subjects affected / exposed	1 / 62 (1.61%)	1 / 58 (1.72%)	4 / 62 (6.45%)
occurrences (all)	1	1	5
Rash			
subjects affected / exposed	12 / 62 (19.35%)	6 / 58 (10.34%)	13 / 62 (20.97%)
occurrences (all)	17	8	14
Pruritus			

subjects affected / exposed	7 / 62 (11.29%)	2 / 58 (3.45%)	4 / 62 (6.45%)
occurrences (all)	7	3	5
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 62 (3.23%)	2 / 58 (3.45%)	8 / 62 (12.90%)
occurrences (all)	3	2	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 62 (25.81%)	7 / 58 (12.07%)	13 / 62 (20.97%)
occurrences (all)	22	14	18
Back pain			
subjects affected / exposed	9 / 62 (14.52%)	10 / 58 (17.24%)	9 / 62 (14.52%)
occurrences (all)	12	10	11
Bone pain			
subjects affected / exposed	1 / 62 (1.61%)	6 / 58 (10.34%)	4 / 62 (6.45%)
occurrences (all)	1	6	4
Neck pain			
subjects affected / exposed	1 / 62 (1.61%)	1 / 58 (1.72%)	4 / 62 (6.45%)
occurrences (all)	1	1	4
Myalgia			
subjects affected / exposed	17 / 62 (27.42%)	11 / 58 (18.97%)	11 / 62 (17.74%)
occurrences (all)	23	13	20
Muscle spasms			
subjects affected / exposed	2 / 62 (3.23%)	5 / 58 (8.62%)	2 / 62 (3.23%)
occurrences (all)	3	6	2
Musculoskeletal chest pain			
subjects affected / exposed	6 / 62 (9.68%)	3 / 58 (5.17%)	4 / 62 (6.45%)
occurrences (all)	6	4	4
Musculoskeletal pain			
subjects affected / exposed	8 / 62 (12.90%)	5 / 58 (8.62%)	10 / 62 (16.13%)
occurrences (all)	11	7	10
Pain in extremity			
subjects affected / exposed	10 / 62 (16.13%)	10 / 58 (17.24%)	12 / 62 (19.35%)
occurrences (all)	14	11	16
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	3 / 62 (4.84%)	3 / 58 (5.17%)	2 / 62 (3.23%)
occurrences (all)	3	3	2
Paronychia			
subjects affected / exposed	4 / 62 (6.45%)	1 / 58 (1.72%)	0 / 62 (0.00%)
occurrences (all)	6	1	0
Oral herpes			
subjects affected / exposed	1 / 62 (1.61%)	5 / 58 (8.62%)	4 / 62 (6.45%)
occurrences (all)	1	5	5
Gastroenteritis			
subjects affected / exposed	0 / 62 (0.00%)	2 / 58 (3.45%)	4 / 62 (6.45%)
occurrences (all)	0	2	4
Gingivitis			
subjects affected / exposed	3 / 62 (4.84%)	1 / 58 (1.72%)	5 / 62 (8.06%)
occurrences (all)	4	1	7
Nasopharyngitis			
subjects affected / exposed	7 / 62 (11.29%)	8 / 58 (13.79%)	10 / 62 (16.13%)
occurrences (all)	9	10	18
Urinary tract infection			
subjects affected / exposed	12 / 62 (19.35%)	10 / 58 (17.24%)	5 / 62 (8.06%)
occurrences (all)	15	12	8
Rhinitis			
subjects affected / exposed	3 / 62 (4.84%)	7 / 58 (12.07%)	6 / 62 (9.68%)
occurrences (all)	3	8	6
Sinusitis			
subjects affected / exposed	2 / 62 (3.23%)	1 / 58 (1.72%)	4 / 62 (6.45%)
occurrences (all)	2	1	9
Upper respiratory tract infection			
subjects affected / exposed	9 / 62 (14.52%)	2 / 58 (3.45%)	8 / 62 (12.90%)
occurrences (all)	10	2	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 62 (19.35%)	9 / 58 (15.52%)	13 / 62 (20.97%)
occurrences (all)	15	14	17
Hypokalaemia			

subjects affected / exposed	6 / 62 (9.68%)	3 / 58 (5.17%)	2 / 62 (3.23%)
occurrences (all)	7	3	2
Hypoalbuminaemia			
subjects affected / exposed	5 / 62 (8.06%)	3 / 58 (5.17%)	1 / 62 (1.61%)
occurrences (all)	7	3	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2010	1) Addition of a third treatment arm (Onar+Pbo+Pac) to help estimate the benefit of onartuzumab+paclitaxel independent of bevacizumab.
21 August 2012	1) Addition of an observation period of 30–60 minutes after completion of each onartuzumab infusion to monitor for infusion-associated symptoms. 2) Clarification that in order to prevent hypersensitivity reactions, all patients should be pre-medicated prior to paclitaxel administration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported