Clinical trial results:
A Randomized, Phase II, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab (MetMAb) in Combination With Paclitaxel + Cisplatin or Carboplatin as First-Line Treatment for Patients With Stage IIIB (T4 Disease) or IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2011-003720-12
Trial protocol	DE GB LV ES IT
Global end of trial date	02 September 2015

Results information

Result version number	v1 (current)
This version publication date	17 September 2016
First version publication date	17 September 2016

Trial information

Trial identification

Sponsor protocol code	GO27820

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01519804
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, 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	02 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a randomized, Phase II, multicenter, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of onartuzumab in combination with paclitaxel + platinum relative to treatment with placebo + paclitaxel + platinum in participants with incurable Stage IIIB (T4 disease) or Stage IV squamous non-small cell lung cancer (NSCLC) in the first-line setting.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) standards and according to the all local laws and regulations concerning clinical study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 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: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Latvia: 16
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	109
EEA total number of subjects	53

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)	43
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening tests and evaluations were performed within 28 days prior to Day 1.

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 + Paclitaxel + Cisplatin/Carboplatin

Arm description:

Onartuzumab was administered in the clinic on Day 1 of each 21-day cycle, up to 4 cycles during induction treatment; if there was no disease progression, maintenance therapy continued until disease progression, unacceptable toxicity, or death, whichever event occurred first. The individual dose of onartuzumab for each participant was 15 milligrams per kilogram (mg/kg) in 250 cubic centimeter (cc) final 0.9 percent (%) normal saline solution (NSS). Paclitaxel was administered IV at a dose of 200 milligrams per meter square (mg/m^2) over 3 hours after the completion of the onartuzumab infusion followed by platinum (cisplatin or carboplatin) every 21 days up to 4 cycles. Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (area under the curve [AUC] 6 mg/mL/min IV) every 21 days up to 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	
Other name	MetMAb
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Onartuzumab was administered in the clinic on Day 1 of each 21-day cycle. The individual dose of onartuzumab for each participant was 15 mg/kg in 250 cc final 0.9% NSS.

Arm title	Placebo + Paclitaxel + Cisplatin/Carboplatin

Arm description:

Placebo matched to onartuzumab was administered in the clinic on Day 1 of each 21-day cycle. Paclitaxel was administered IV at a dose of 200 mg/m^2 over 3 hours after the completion of the placebo infusion followed by platinum (cisplatin or carboplatin). Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (AUC 6 mg/mL/min IV) every 21 days up to 4 cycles.

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

Dosage and administration details:

Placebo matched to onartuzumab was administered in the clinic on Day 1 of each 21-day cycle.

Number of subjects in period 1	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin
Started	55	54
Completed	0	0
Not completed	55	54
Consent withdrawn by subject	2	2
Study Terminated By Sponsor	15	18
Death	36	33
Lost to follow-up	2	1

Baseline characteristics

Reporting groups

Reporting group title	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin

Reporting group description:

Onartuzumab was administered in the clinic on Day 1 of each 21-day cycle, up to 4 cycles during induction treatment; if there was no disease progression, maintenance therapy continued until disease progression, unacceptable toxicity, or death, whichever event occurred first. The individual dose of onartuzumab for each participant was 15 milligrams per kilogram (mg/kg) in 250 cubic centimeter (cc) final 0.9 percent (%) normal saline solution (NSS). Paclitaxel was administered IV at a dose of 200 milligrams per meter square (mg/m^2) over 3 hours after the completion of the onartuzumab infusion followed by platinum (cisplatin or carboplatin) every 21 days up to 4 cycles. Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (area under the curve [AUC] 6 mg/mL/min IV) every 21 days up to 4 cycles.

Reporting group title	Placebo + Paclitaxel + Cisplatin/Carboplatin

Reporting group description:

Placebo matched to onartuzumab was administered in the clinic on Day 1 of each 21-day cycle. Paclitaxel was administered IV at a dose of 200 mg/m^2 over 3 hours after the completion of the placebo infusion followed by platinum (cisplatin or carboplatin). Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (AUC 6 mg/mL/min IV) every 21 days up to 4 cycles.

Reporting group values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin	Total
Number of subjects	55	54	109
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 67.1 ± 8.2	 66.2 ± 9.2	 -
Gender categorical Units: Subjects			
Female	16	14	30
Male	39	40	79

End points

End points reporting groups

Reporting group title	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin

Reporting group description:

Onartuzumab was administered in the clinic on Day 1 of each 21-day cycle, up to 4 cycles during induction treatment; if there was no disease progression, maintenance therapy continued until disease progression, unacceptable toxicity, or death, whichever event occurred first. The individual dose of onartuzumab for each participant was 15 milligrams per kilogram (mg/kg) in 250 cubic centimeter (cc) final 0.9 percent (%) normal saline solution (NSS). Paclitaxel was administered IV at a dose of 200 milligrams per meter square (mg/m^2) over 3 hours after the completion of the onartuzumab infusion followed by platinum (cisplatin or carboplatin) every 21 days up to 4 cycles. Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (area under the curve [AUC] 6 mg/mL/min IV) every 21 days up to 4 cycles.

Reporting group title	Placebo + Paclitaxel + Cisplatin/Carboplatin

Reporting group description:

Placebo matched to onartuzumab was administered in the clinic on Day 1 of each 21-day cycle. Paclitaxel was administered IV at a dose of 200 mg/m^2 over 3 hours after the completion of the placebo infusion followed by platinum (cisplatin or carboplatin). Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (AUC 6 mg/mL/min IV) every 21 days up to 4 cycles.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1]

End point description:

PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression was determined based on investigator assessment with use of Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. PFS was to be estimated using Kaplan-Meier method. Progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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	Primary

End point timeframe:

Baseline, every 6 weeks (±7 days) during the first 4 cycles (each cycle was 21 days) of treatment, then every 9 weeks (±7 days) during the maintenance treatment until disease progression or death (maximum up to approximately 32 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[2] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[3] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Primary: PFS: Subgroup of Participants With Met Diagnostic-Positive Squamous NSCLC

End point title	PFS: Subgroup of Participants With Met Diagnostic-Positive Squamous NSCLC[4]

End point description:

PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression was determined based on investigator assessment with use of RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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). PFS was to be estimated using Kaplan-Meier method.

End point type	Primary

End point timeframe:

Baseline, every 6 weeks (±7 days) during the first 4 cycles (each cycle was 21 days) of treatment, then every 9 weeks (±7 days) during the maintenance treatment until disease progression or death (maximum up to approximately 32 months).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[6] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization until death due to any cause.

End point type	Secondary

End point timeframe:

From baseline until death (maximum up to approximately 32 months).

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[8] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response

End point title	Percentage of Participants With Objective Response

End point description:

Objective response (OR) is defined as a complete response (CR) or partial response (PR). OR is measured using RECIST v1.1. Participants without a post-baseline tumor assessment were considered as non-responders.
CR: Disappearance of all target and non-target lesions and normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimeter (mm);

PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

Baseline, every 6 weeks (±7 days) during the first 4 cycles (each cycle was 21 days) of treatment, then every 9 weeks (±7 days) during the maintenance treatment until disease progression or death (maximum up to approximately 32 months).

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: percentage of participants				
number (not applicable)				

Notes:

[9] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[10] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)

End point description:

OR is defined as a CR or PR. OR is measured using RECIST v1.1. DOR: time from the first occurrence of a documented OR to disease progression (as determined by the investigator using RECIST v1.1) or death from any cause during the study. Participants without a postbaseline tumor assessment were considered as nonresponders. OR was not evaluated due to discontinuation of the clinical development of onartuzumab. CR: Disappearance of all target and non-target lesions and normalization of tumor marker levels. 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 diameters.

End point type	Secondary

End point timeframe:

Baseline, every 6 weeks (±7 days) during the first 4 cycles (each cycle was 21 days) of treatment, then every 9 weeks (±7 days) during the maintenance treatment until disease progression or death (maximum up to approximately 32 months)

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[11] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[12] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control

End point title	Percentage of Participants With Disease Control

End point description:

Disease control rate was defined as the rate of participants with CR, PR, or stable disease (SD) maintained for ≥6 weeks. CR: Disappearance of all target and non-target lesions and normalization of tumor marker levels. 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 diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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:

Baseline, every 6 weeks (±7 days) during the first 4 cycles (each cycle was 21 days) of treatment, then every 9 weeks (±7 days) during the maintenance treatment until disease progression or death (maximum up to approximately 32 months).

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: percentage of participants				
number (not applicable)				

Notes:

[13] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

[14] - Endpoint was not evaluated due to early study termination primarily because of limited efficacy.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration for Onartuzumab

End point title	Maximum Serum Concentration for Onartuzumab[15]

End point description:

Maximum serum concentration is expressed in micrograms per milliliter (mcg/mL). Safety population included all participants who were randomized and had received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Predose (within 1 hour), 30 minutes postdose on Day 1 of Cycle 4 (each cycle was 21 days)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint does not apply to the arm group 2 (Placebo arm).

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: mcg/mL				
arithmetic mean (standard deviation)	452 (± 112)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration for Onartuzumab

End point title	Minimum Serum Concentration for Onartuzumab[16]

End point description:

Minimum serum concentration is expressed in micrograms per milliliter (mcg/mL). Safety population

End point type	Secondary

End point timeframe:

Predose (within 1 hour) on Day 1 of Cycle 4 (each cycle was 21 days)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint does not apply to the arm group 2 (Placebo arm).

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: mcg/mL				
arithmetic mean (standard deviation)	63.7 (± 23.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentrations for Paclitaxel

End point title	Maximum Serum Concentrations for Paclitaxel

End point description:

For paclitaxel PK, only samples from 1 participant from the onartuzumab treatment arm were collected and analyzed. As these data are very limited, no PK parameters were calculated for Paclitaxel.

End point type	Secondary

End point timeframe:

Prior to first chemotherapy drug infusion (within 1 hour), 0-10 minutes, 2 hour (±30 minutes), 5, and 6 hour after end of paclitaxel infusion on Day 1 of induction Cycles 1 and 4 (each cycle was 21 days). Paclitaxel infusion was administered over 3 hours.

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: mcg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[17] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

[18] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Curve From Time 0 to t (AUC[0-t]) For Platinum and Ultrafilterable Platinum

End point title	Area Under Curve From Time 0 to t (AUC[0-t]) For Platinum and Ultrafilterable Platinum

End point description:

AUC(0-t) was to be expressed in micrograms times (*) hour per milliliter (mcg*hour/mL). For platinum PK, only samples from 1 participant from the onartuzumab treatment arm were collected and analyzed. As these data are very limited, no PK parameters were calculated for platinum.

End point type	Secondary

End point timeframe:

Prior to first chemotherapy drug infusion (within 1 hour), 0–5 minute, 1 hour (±15 minute), 3, and 6 hour after end of cisplatin (1-2 hours) or carboplatin (30-60 minutes) infusion on Day 1 of induction Cycles 1 and 4 (each cycle was 21 days)

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: mcg*hour/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[19] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

[20] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-t) For Paclitaxel

End point title	AUC(0-t) For Paclitaxel

End point description:

For paclitaxel PK, only samples from 1 participant from the onartuzumab treatment arm were collected and analyzed. As these data are very limited, no PK parameters were calculated for Paclitaxel.

End point type	Secondary

End point timeframe:

Prior to first chemotherapy drug infusion (within 1 hour), 0-10 minutes, 2 hour (±30 minutes), 5, and 6 hour after end of paclitaxel infusion on Day 1 of induction Cycles 1 and 4 (each cycle was 21 days). Paclitaxel infusion was administered over 3 hours.

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: mcg*hour/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[21] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

[22] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration for Platinum and Ultrafilterable Platinum

End point title	Maximum Serum Concentration for Platinum and Ultrafilterable Platinum

End point description:

For platinum PK, only samples from 1 participant from the onartuzumab treatment arm were collected and analyzed. As these data are very limited, no PK parameters were calculated for platinum.

End point type	Secondary

End point timeframe:

Prior to first chemotherapy drug infusion (within 1 hour), 0–5 minute, 1 hour (±15 minute), 3, and 6 hour after end of cisplatin (12 hours) or carboplatin (3060 minutes) infusion on Day 1 of induction Cycles 1 and 4 (each cycle was 21 days)

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[23]	0[24]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[23] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

[24] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with anti-therapeutic antibody against onartuzumab

End point title	Percentage of Participants with anti-therapeutic antibody against onartuzumab

End point description:

End point type	Secondary

End point timeframe:

Onartuzumab pre-dose (within 1 hour) on Day 1 of induction Cycles 1 and 4 (each cycle was 21 days), and on study drug discontinuation visit (maximum up to approximately 32 months)

End point values	Onartuzumab + Paclitaxel + Cisplatin/Carboplatin	Placebo + Paclitaxel + Cisplatin/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[25]	0[26]		
Units: Percentage of participants				

number (not applicable)				

Notes:

[25] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

[26] - Endpoint was not evaluated due to insufficient number of participants (<50%) with data.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Basline up to 32 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Onartuzumab + Paclitaxel + Platinum Arm

Reporting group description:

Onartuzumab was administered in the clinic on Day 1 of each 21-day cycle. The individual dose of onartuzumab for each participant was 15 mg/kg in 250 cc final 0.9% NSS. Paclitaxel was administered IV at a dose of 200 mg/m^2 over 3 hours after the completion of the onartuzumab infusion followed by platinum (cisplatin or carboplatin). Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (AUC 6 IV) every 21 days up to 4 cycles.

Reporting group title	Placebo + Paclitaxel + Platinum Arm

Reporting group description:

Placebo was administered in the clinic on Day 1 of each 21-day cycle. The individual dose of placebo for each participant was 15 mg/kg in 250 cc final 0.9% NSS. Paclitaxel was administered IV at a dose of 200 mg/m^2 over 3 hours after the completion of the placebo infusion followed by platinum (cisplatin or carboplatin). Cisplatin IV infusion was administered 30 minutes after completion of the paclitaxel infusion at a dose of 75 mg/m^2 over 1 − 2 hours every 21 days up to 4 cycles or per standard of care at the institution or carboplatin (AUC 6 IV) every 21 days up to 4 cycles.

Serious adverse events	Onartuzumab + Paclitaxel + Platinum Arm	Placebo + Paclitaxel + Platinum Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 54 (40.74%)	17 / 52 (32.69%)	
number of deaths (all causes)	36	33	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic Pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Orthostatic Hypotension			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infusion Site Extravasation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural Effusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 54 (3.70%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight Decreased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 54 (1.85%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac Failure			
subjects affected / exposed	1 / 54 (1.85%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial Effusion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids Thrombosed			

subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated Umbilical Hernia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enterocolitis Infectious			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 54 (7.41%)	4 / 52 (7.69%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post Procedural Cellulitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Onartuzumab + Paclitaxel + Platinum Arm	Placebo + Paclitaxel + Platinum Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 54 (96.30%)	48 / 52 (92.31%)	
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Neutrophil Count Decreased			
subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Weight Decreased			
subjects affected / exposed	6 / 54 (11.11%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Weight Increased			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	4 / 54 (7.41%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Hypertension			
subjects affected / exposed	3 / 54 (5.56%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
Hypotension			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Nervous system disorders			
Dizziness			

subjects affected / exposed	5 / 54 (9.26%)	6 / 52 (11.54%)	
occurrences (all)	5	7	
Dysgeusia			
subjects affected / exposed	2 / 54 (3.70%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Headache			
subjects affected / exposed	6 / 54 (11.11%)	2 / 52 (3.85%)	
occurrences (all)	12	2	
Neuropathy Peripheral			
subjects affected / exposed	13 / 54 (24.07%)	10 / 52 (19.23%)	
occurrences (all)	14	14	
Paraesthesia			
subjects affected / exposed	5 / 54 (9.26%)	4 / 52 (7.69%)	
occurrences (all)	7	4	
Peripheral Sensory Neuropathy			
subjects affected / exposed	7 / 54 (12.96%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Polyneuropathy			
subjects affected / exposed	3 / 54 (5.56%)	4 / 52 (7.69%)	
occurrences (all)	3	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 54 (29.63%)	11 / 52 (21.15%)	
occurrences (all)	18	11	
Neutropenia			
subjects affected / exposed	10 / 54 (18.52%)	7 / 52 (13.46%)	
occurrences (all)	19	10	
Thrombocytopenia			
subjects affected / exposed	9 / 54 (16.67%)	3 / 52 (5.77%)	
occurrences (all)	14	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 54 (14.81%)	13 / 52 (25.00%)	
occurrences (all)	13	15	
Chest Pain			

subjects affected / exposed	3 / 54 (5.56%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	22 / 54 (40.74%)	15 / 52 (28.85%)	
occurrences (all)	23	18	
Mucosal Inflammation			
subjects affected / exposed	1 / 54 (1.85%)	4 / 52 (7.69%)	
occurrences (all)	1	4	
Oedema Peripheral			
subjects affected / exposed	20 / 54 (37.04%)	1 / 52 (1.92%)	
occurrences (all)	26	1	
Pain			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Peripheral Swelling			
subjects affected / exposed	4 / 54 (7.41%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Pyrexia			
subjects affected / exposed	4 / 54 (7.41%)	6 / 52 (11.54%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	14 / 54 (25.93%)	6 / 52 (11.54%)	
occurrences (all)	15	8	
Diarrhoea			
subjects affected / exposed	12 / 54 (22.22%)	13 / 52 (25.00%)	
occurrences (all)	13	17	
Nausea			
subjects affected / exposed	24 / 54 (44.44%)	12 / 52 (23.08%)	
occurrences (all)	40	12	
Stomatitis			
subjects affected / exposed	3 / 54 (5.56%)	2 / 52 (3.85%)	
occurrences (all)	4	2	

Vomiting			
subjects affected / exposed	7 / 54 (12.96%)	6 / 52 (11.54%)	
occurrences (all)	9	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 54 (16.67%)	9 / 52 (17.31%)	
occurrences (all)	9	9	
Dyspnoea			
subjects affected / exposed	11 / 54 (20.37%)	6 / 52 (11.54%)	
occurrences (all)	11	6	
Epistaxis			
subjects affected / exposed	0 / 54 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Haemoptysis			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Oropharyngeal Pain			
subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 54 (55.56%)	23 / 52 (44.23%)	
occurrences (all)	30	23	
Night Sweats			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	5	2	
Rash			
subjects affected / exposed	10 / 54 (18.52%)	3 / 52 (5.77%)	
occurrences (all)	11	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 54 (11.11%)	0 / 52 (0.00%)	
occurrences (all)	6	0	
Depression			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	3	

Insomnia			
subjects affected / exposed	7 / 54 (12.96%)	6 / 52 (11.54%)	
occurrences (all)	7	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 54 (7.41%)	8 / 52 (15.38%)	
occurrences (all)	5	11	
Back pain			
subjects affected / exposed	5 / 54 (9.26%)	7 / 52 (13.46%)	
occurrences (all)	5	7	
Bone Pain			
subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	4	2	
Muscle Spasms			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Musculoskeletal Chest Pain			
subjects affected / exposed	3 / 54 (5.56%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Musculoskeletal Pain			
subjects affected / exposed	6 / 54 (11.11%)	3 / 52 (5.77%)	
occurrences (all)	9	3	
Myalgia			
subjects affected / exposed	8 / 54 (14.81%)	7 / 52 (13.46%)	
occurrences (all)	16	13	
Pain In Extremity			
subjects affected / exposed	9 / 54 (16.67%)	5 / 52 (9.62%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	11 / 54 (20.37%)	13 / 52 (25.00%)	
occurrences (all)	12	13	
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	4	
Hyperglycaemia			

subjects affected / exposed	6 / 54 (11.11%)	3 / 52 (5.77%)	
occurrences (all)	8	3	
Hyperkalaemia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	6 / 54 (11.11%)	1 / 52 (1.92%)	
occurrences (all)	8	1	
Hypomagnesaemia			
subjects affected / exposed	6 / 54 (11.11%)	4 / 52 (7.69%)	
occurrences (all)	7	4	
Hyponatraemia			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	Protocol was amended for the following reasons: The infusion time for onartuzumab/placebo and carboplatin was clarified. The correction for the Cockcroft-Gault method for calculation of creatinine clearance in females (for carboplatin dose calculation), was provided. For participants who consented to additional pharmacokinetic (PK) sampling, the timepoint for plasma paclitaxel PK 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.
13 April 2012	Protocol has been amended for the following reasons: The study exclusion criterion regarding participants with EGFR-activating mutations who are suitable for anti-EGFR therapy has been modified to allow for cases where treatment is unavailable to or refused by the patient. It has been clarified that baseline weight (rather than screening weight) will be used to calculate onartuzumab/placebo dosage. The timing of carboplatin treatment after paclitaxel infusion has been clarified. The maximum allowed onartuzumab/placebo dose delay has been extended from 7 days to one treatment cycle. Several chemotherapy dose modification tables have been modified for consistency with the accompanying text. To more fully comply with updated regulations, serious adverse events (SAEs) and pregnancies should be reported within 24 hours rather than 1 working day; this change has been reflected throughout. The number of patients and study sites has been corrected. Baseline hematology and chemistry laboratory assessments will not have to be repeated at Cycle 1 Day 1 if the assessments were performed within 3 days before Cycle 1 Day 1. During survival follow-up, the requirement for the reporting of non-serious adverse events has been removed; only SAEs considered related to study treatments need to be reported.
26 June 2013	Protocol was amended for the following reasons: For the Sponsor’s internal decision-making process, a third data review by the Internal Monitoring Committee (IMC) has been added to assess the treatment effect in participants with Met diagnostic positive tumors at an earlier time point than the planned final analysis. No crossover from placebo to onartuzumab treatment was allowed in this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Sponsor made a decision to discontinue further clinical development of onartuzumab due to the limited efficacy observed in the conduct of this study and was not based on safety-related issues.

Notes: