Clinical trial results:
A Randomized, Open-Label, Phase II Study Assessing the Efficacy and the Safety of Bevacizumab in Neoadjuvant Therapy in Patients With Figo Stage IIIC/IV Ovarian, Tubal or Peritoneal Adenocarcinoma, Initially Unresectable

Summary

EudraCT number	2012-001144-22
Trial protocol	FR
Global end of trial date	17 August 2016

Results information

Result version number	v1 (current)
This version publication date	31 August 2017
First version publication date	31 August 2017

Trial information

Trial identification

Sponsor protocol code	ML28337

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01739218
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of neoadjuvant bevacizumab and chemotherapy measured by the complete resection rate after interval debulking surgery (IDS)

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised by subsequent amendments, following International Conference of Harmonization (ICH) recommendations, the French law, "Loi Huriet" (Law dated December 20, 1988) and the Law No 78-17 namely "Loi informatique et liberté" (Information and Freedom law). This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law, and to follow ICH good clinical practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	29 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	59

From 65 to 84 years	35
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 99 participants were randomized in the study, and 95 participants received at least one dose of any study treatment.

Pre-assignment

Screening details:

Four participants were randomized to "Carboplatin + Paclitaxel + Bevacizumab" arm, but did not receive any study treatment (3 participants due to protocol violation and 1 participant due to consent withdrawal).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Carboplatin + Paclitaxel

Arm description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered only during the adjuvant treatment period in Cycles 6 to 26.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered at a dose calculated according to the Calvert formula ([participant's glomerular filtration rate + 25] multiplied by the target area under the concentration-time curve [AUC] of 5 milligrams per milliliter per minute [mg/mL/min]), as intravenous [IV] infusion over 30-60 minutes [min] every 3 weeks).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at a dose of 15 milligrams per kilogram [mg/kg] as IV infusion over 30-90 min every 3 weeks.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 175 milligrams per meter-squared [mg/m^2] as IV infusion

over 3 hours using a rate controlling device every 3 weeks, or at a dose of 80 mg/m^2 as IV infusion over 1 hour using a rate controlling device every week (only during Cycles 5 to 8).

Arm title	Carboplatin + Paclitaxel + Bevacizumab

Arm description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered during both the neoadjuvant and adjuvant treatment periods in Cycles 1 to 26 (no treatment in Cycles 4 and 5).

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered at a dose calculated according to the Calvert formula ([participant's glomerular filtration rate + 25] multiplied by the target AUC of 5 mg/mL/min), as IV infusion over 30-60 min every 3 weeks.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at a dose of 15 milligrams per kilogram [mg/kg] as IV infusion over 30-90 min every 3 weeks.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 175 mg/m^2 as IV infusion over 3 hours using a rate controlling device every 3 weeks, or at a dose of 80 mg/m^2 as IV infusion over 1 hour using a rate controlling device every week (only during Cycles 5 to 8).

Number of subjects in period 1	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab
Started	37	58
Completed	4	11
Not completed	33	47
Physician decision	3	8
Consent withdrawn by subject	2	4
Disease progression	23	30

Death	2	-
Adverse event	1	-
Lost to follow-up	1	-
Protocol deviation	1	5

Baseline characteristics

Reporting groups

Reporting group title	Carboplatin + Paclitaxel

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered only during the adjuvant treatment period in Cycles 6 to 26.

Reporting group title	Carboplatin + Paclitaxel + Bevacizumab

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered during both the neoadjuvant and adjuvant treatment periods in Cycles 1 to 26 (no treatment in Cycles 4 and 5).

Reporting group values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab	Total
Number of subjects	37	58	95
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	61.3	62.3	
standard deviation	± 9.6	± 9.6	-
Gender Categorical Units: Subjects			
Female	37	58	95
Male	0	0	0

End points

End points reporting groups

Reporting group title	Carboplatin + Paclitaxel

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered only during the adjuvant treatment period in Cycles 6 to 26.

Reporting group title	Carboplatin + Paclitaxel + Bevacizumab

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered during both the neoadjuvant and adjuvant treatment periods in Cycles 1 to 26 (no treatment in Cycles 4 and 5).

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified intent-to-treat (mITT) population included all randomized participants who received at least one dose of any component of study treatment (bevacizumab, paclitaxel or carboplatin). Participants were grouped according to their initially assigned treatment.

Primary: Percentage of Participants With Complete Resection After IDS

End point title	Percentage of Participants With Complete Resection After IDS[1]

End point description:

Complete resection is defined as removal of all macroscopic residual tumor at IDS, that is completeness of cytoreduction (CC) score = 0. The CC score indicates quantity of malignancy that remains following surgery. A CC score of 0 = no tumor visualization after the complete resection; 1 = residual tumor nodules less than 0.5 centimeters (cm) in diameter; 2 = residual tumor nodules between 0.5 cm and 5 cm in diameter; and 3 = residual tumor nodules greater than 5 cm in diameter, or a layer of disease that is not completely peritonectomized. Participants with missing CC score, or without IDS were considered as failure. The percentage of participants with complete resection and associated 95% one-sided confidence interval (CI) was assessed using Pearson-Clopper's exact method. Analysis was performed on mITT population. The value "99999" in results indicates that as planned higher side of CI was not calculated.

End point type	Primary

End point timeframe:

After IDS (approximately 4 months from randomization)

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: percentage of participants				
number (confidence interval 95%)	51.4 (36.8 to 99999)	58.6 (47 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Different CC Scores After IDS

End point title	Percentage of Participants With Different CC Scores After IDS[2]

End point description:

The CC score indicates quantity of malignancy that remains following surgery. A CC score of 0 = no tumor visualization after the complete resection; 1 = residual tumor nodules less than (<) 0.5 cm in diameter; 2 = residual tumor nodules between 0.5 cm and 5 cm in diameter; and 3 = residual tumor nodules greater than (>) 5 cm in diameter, or a layer of disease that is not completely peritonectomized. Analysis was performed on mITT population. Here, 'Number of Subjects Analysed' signifies the number of participants who underwent IDS.

End point type	Primary

End point timeframe:

After IDS (approximately 4 months from randomization)

Notes:

[2] - 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	40		
Units: percentage of participants				
number (not applicable)				
CC Score = 0	86.4	85		
CC Score = 1	9.1	7.5		
CC Score = 2	4.5	2.5		
CC Score = 3	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Percentage of Participants with Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

Objective response was defined as percentage of participants with a confirmed complete response (CR) or partial response (PR) assessed according to RECIST v1.1. Target lesions (TLs) were selected based on their size (those with the longest diameter) and their suitability for accurate repeated measurements.

Measurable pathological nodes with short axis (SA) of greater than or equal to (>/=) 15 millimeter (mm) were also identified as TLs. All other lesions (or sites of disease) were identified as non-TLs. CR was defined as disappearance of all TLs/non-TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30 percent (%) decrease in sum of diameters (SD) of TLs, taking as reference the baseline SD, and persistence of >/=1 non-TLs. Confirmation of response at a consecutive tumor assessment >/=4 weeks apart was required. Analysis was performed on mITT population. Participants without tumor assessment after start of study treatment were considered as non-responders.

End point type	Secondary

End point timeframe:

At IDS (approximately 3 months); at Cycle 26 (approximately 22 months); and at last tumor assessment (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: percentage of participants				
number (not applicable)				
At IDS	62.2	67.2		
At Cycle 26	18.9	19		
At Last Tumor Assessment	21.6	36.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Response According to Cancer Antigen (CA)-125 Levels

End point title	Percentage of Participants with Response According to Cancer Antigen (CA)-125 Levels

End point description:

The CA-125 response was defined as >/=50% reduction in CA-125 level from baseline and confirmation and maintenance of this reduction at the next visit. Analysis was performed on mITT population. Only participants with a baseline value >/=70 units per milliliter (U/mL) were included in this analysis. Last observation carried forward method (LOCF) was used in case of missing values at last CA-125 assessment. Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point for different arms, respectively.

End point type	Secondary

End point timeframe:

At IDS (approximately 3 months); at Cycle 26 (approximately 22 months); and at last CA-125 assessment (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	58		
Units: percentage of participants				
number (not applicable)				
At IDS (n=36,58)	80.6	87.9		
At Cycle 26 (n=7,14)	100	92.9		
At Last CA-125 Assessment (n=36,58)	69.4	63.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with RECIST v1.1 Objective Response and CA-125 Response

End point title	Percentage of Participants with RECIST v1.1 Objective Response and CA-125 Response

End point description:

Objective response was defined as percentage of participants with a CR or PR according to RECIST v1.1. CR was defined as the disappearance of all TLs/non-TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30% decrease in SD of TLs, taking as reference the baseline SD, and persistence of 1 or more non-TLs. Confirmation of response at a consecutive tumor assessment >/=4 weeks apart was required. The CA-125 response was defined as >/=50% reduction in CA-125 level from baseline and confirmation and maintenance of this reduction at the next visit. The response according to RECIST v1.1 and CA-125 level was derived, at a given visit, only if the delay between tumor assessment and CA-125 sample was less than or equal to (</=) 28 days. Analysis was performed on mITT population. LOCF method was used in case of missing values at last response assessment. Here, 'n' signifies the number of participants evaluable at specified time point for different arms, respectively.

End point type	Secondary

End point timeframe:

At Cycle 26 (approximately 22 months) and at last response assessment (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: percentage of participants				
number (not applicable)				
At Cycle 26 (n=7,12)	100	75		
At Last Response Assessment (n=37,58)	16.2	27.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with RECIST v1.1 Objective Response Without CA-125 Response

End point title	Percentage of Participants with RECIST v1.1 Objective Response Without CA-125 Response

End point description:

Objective response was defined as percentage of participants with a CR or PR according to RECIST v1.1. CR was defined as the disappearance of all TLs/non-TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30% decrease in SD of TLs, taking as reference the baseline SD, and persistence of 1 or more non-TLs. Confirmation of response at a consecutive tumor assessment >/=4 weeks apart was required. The CA-125 response was defined as >/=50% reduction in CA-125 level from baseline and confirmation and maintenance of this reduction at the next visit. The response according to RECIST v1.1 and CA-125 level was derived, at a given visit, only if the delay between tumor assessment and CA-125 sample was </=28 days. Analysis was performed on mITT population. LOCF method was used in case of missing values at last response assessment. Here, 'n' signifies the number of participants evaluable at specified time point for different arms, respectively.

End point type	Secondary

End point timeframe:

At Cycle 26 (approximately 22 months) and at last response assessment (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: percentage of participants				
number (not applicable)				
At Cycle 26 (n=7,12)	0	8.3		
At Last Response Assessment (n=37,58)	5.4	8.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CA-125 Response Without RECIST v1.1 Objective Response

End point title	Percentage of Participants with CA-125 Response Without RECIST v1.1 Objective Response

End point description:

Objective response was defined as percentage of participants with a CR or PR according to RECIST v1.1. CR was defined as the disappearance of all TLs/non-TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30% decrease in SD of TLs, taking as reference the baseline SD, and persistence of 1 or more non-TLs. Confirmation of response at a consecutive tumor assessment >/=4 weeks apart was required. The CA-125 response was defined as >/=50% reduction in CA-125 level from baseline and confirmation and maintenance of this reduction at the next visit. The response according to RECIST v1.1 and CA-125 level was derived, at a given visit, only if the delay between tumor assessment and CA-125 sample was </=28 days. Analysis was performed on mITT population. LOCF method was used in case of missing values at last response assessment. Here, 'n' signifies the number of participants evaluable at specified time point for different arms, respectively.

End point type	Secondary

End point timeframe:

At Cycle 26 (approximately 22 months) and at last response assessment (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: percentage of participants				
number (not applicable)				
At Cycle 26 (n=7,12)	0	16.7		
At Last Response Assessment (n=37,58)	54.1	36.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Disease Progression or Death From any Cause

End point title	Number of Participants With Disease Progression or Death From any Cause

End point description:

Progressive disease (PD) was defined as >/=20% relative increase and >/=5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

From Baseline to disease progression or death due to any cause (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: participants				
number (not applicable)	24	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to RECIST v1.1

End point title	Progression-Free Survival (PFS) According to RECIST v1.1

End point description:

PFS was defined as the time from first intake of any study medication until the first radiographically documented PD assessed using RECIST v1.1 criteria or death from any cause, whichever occurred first. Participants with no PFS events were censored at the time of the last evaluable tumor assessment. Participants with no tumor assessment at and after the baseline visit were censored on the date of first study treatment. PD was defined as >/=20% relative increase and >/=5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The median PFS (with the associated 95% CI) was estimated using the Kaplan-Meier method. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

From Baseline to disease progression or death due to any cause (up to approximately 38 months)

End point values	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	58		
Units: months				
median (confidence interval 95%)	21.2 (14.5 to 26.7)	23.5 (18.5 to 30.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (SAEs): from randomization up to last assessment (up to approximately 38 months); non-SAEs: from Day 1 up to 28 days after last dose (up to approximately 23 months)

Adverse event reporting additional description:

Analysis was performed on safety (SAF) population, which included all participants who received at least one dose of any component of study treatment (bevacizumab, paclitaxel or carboplatin). Participants were grouped according to the treatment actually received. Events related to treatment indicate bevacizumab-related events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Carboplatin + Paclitaxel + Bevacizumab

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered during both the neoadjuvant and adjuvant treatment periods in Cycles 1 to 26 (no treatment in Cycles 4 and 5).

Reporting group title	Carboplatin + Paclitaxel

Reporting group description:

Participants received 4 cycles of neoadjuvant therapy prior to IDS (performed 28 days after the last neoadjuvant course if resectable tumor; participants with unresectable tumor went through follow-up period) and 22 cycles of adjuvant therapy before entering long-term follow-up (28 days after last treatment administration and every 6 months until disease progression or study end [maximum up to 38 months]). Each cycle was 3 weeks in length. Carboplatin and paclitaxel were administered during Cycles 1 to 8. Bevacizumab was administered only during the adjuvant treatment period in Cycles 6 to 26.

Serious adverse events	Carboplatin + Paclitaxel + Bevacizumab	Carboplatin + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 55 (38.18%)	18 / 40 (45.00%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (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	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 55 (1.82%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 55 (5.45%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum perforation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (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			
Femur fracture			

subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (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	2 / 55 (3.64%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 55 (3.64%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 55 (3.64%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 55 (5.45%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 55 (1.82%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 55 (1.82%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 55 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			

subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoiditis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal ischaemia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infected lymphocele			
subjects affected / exposed	2 / 55 (3.64%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			

subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (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	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 55 (3.64%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 55 (0.00%)	1 / 40 (2.50%)	
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	Carboplatin + Paclitaxel + Bevacizumab	Carboplatin + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 55 (100.00%)	39 / 40 (97.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 55 (38.18%)	9 / 40 (22.50%)	
occurrences (all)	23	11	
Hot flush			
subjects affected / exposed	5 / 55 (9.09%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Lymphocele			
subjects affected / exposed	4 / 55 (7.27%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	38 / 55 (69.09%)	22 / 40 (55.00%)	
occurrences (all)	55	46	
Oedema peripheral			
subjects affected / exposed	8 / 55 (14.55%)	6 / 40 (15.00%)	
occurrences (all)	9	7	
Impaired healing			
subjects affected / exposed	8 / 55 (14.55%)	5 / 40 (12.50%)	
occurrences (all)	10	6	
Fatigue			

subjects affected / exposed	6 / 55 (10.91%)	4 / 40 (10.00%)	
occurrences (all)	8	5	
Mucosal inflammation			
subjects affected / exposed	8 / 55 (14.55%)	2 / 40 (5.00%)	
occurrences (all)	11	4	
Pain			
subjects affected / exposed	6 / 55 (10.91%)	3 / 40 (7.50%)	
occurrences (all)	6	3	
Pyrexia			
subjects affected / exposed	5 / 55 (9.09%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	6 / 55 (10.91%)	1 / 40 (2.50%)	
occurrences (all)	6	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	29 / 55 (52.73%)	8 / 40 (20.00%)	
occurrences (all)	44	10	
Dyspnoea			
subjects affected / exposed	8 / 55 (14.55%)	4 / 40 (10.00%)	
occurrences (all)	9	6	
Cough			
subjects affected / exposed	8 / 55 (14.55%)	2 / 40 (5.00%)	
occurrences (all)	10	3	
Dysphonia			
subjects affected / exposed	7 / 55 (12.73%)	2 / 40 (5.00%)	
occurrences (all)	7	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 55 (9.09%)	2 / 40 (5.00%)	
occurrences (all)	6	3	
Anxiety			
subjects affected / exposed	4 / 55 (7.27%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Investigations			

Weight decreased			
subjects affected / exposed	8 / 55 (14.55%)	3 / 40 (7.50%)	
occurrences (all)	8	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 55 (7.27%)	2 / 40 (5.00%)	
occurrences (all)	6	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 55 (3.64%)	4 / 40 (10.00%)	
occurrences (all)	2	5	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	25 / 55 (45.45%)	18 / 40 (45.00%)	
occurrences (all)	27	23	
Paraesthesia			
subjects affected / exposed	9 / 55 (16.36%)	4 / 40 (10.00%)	
occurrences (all)	13	4	
Headache			
subjects affected / exposed	11 / 55 (20.00%)	6 / 40 (15.00%)	
occurrences (all)	18	6	
Dysgeusia			
subjects affected / exposed	4 / 55 (7.27%)	5 / 40 (12.50%)	
occurrences (all)	4	6	
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 55 (10.91%)	2 / 40 (5.00%)	
occurrences (all)	10	4	
Dysaesthesia			
subjects affected / exposed	3 / 55 (5.45%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Neurotoxicity			
subjects affected / exposed	5 / 55 (9.09%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 55 (45.45%)	24 / 40 (60.00%)	
occurrences (all)	30	27	
Neutropenia			

subjects affected / exposed	21 / 55 (38.18%)	16 / 40 (40.00%)	
occurrences (all)	37	24	
Thrombocytopenia			
subjects affected / exposed	11 / 55 (20.00%)	12 / 40 (30.00%)	
occurrences (all)	20	23	
Lymphopenia			
subjects affected / exposed	3 / 55 (5.45%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 55 (5.45%)	2 / 40 (5.00%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	29 / 55 (52.73%)	18 / 40 (45.00%)	
occurrences (all)	39	27	
Nausea			
subjects affected / exposed	35 / 55 (63.64%)	22 / 40 (55.00%)	
occurrences (all)	62	50	
Constipation			
subjects affected / exposed	25 / 55 (45.45%)	17 / 40 (42.50%)	
occurrences (all)	44	25	
Diarrhoea			
subjects affected / exposed	20 / 55 (36.36%)	13 / 40 (32.50%)	
occurrences (all)	34	20	
Vomiting			
subjects affected / exposed	17 / 55 (30.91%)	14 / 40 (35.00%)	
occurrences (all)	20	21	
Abdominal pain upper			
subjects affected / exposed	5 / 55 (9.09%)	10 / 40 (25.00%)	
occurrences (all)	5	14	
Gastrointestinal motility disorder			
subjects affected / exposed	6 / 55 (10.91%)	4 / 40 (10.00%)	
occurrences (all)	6	4	
Gingival bleeding			

subjects affected / exposed	6 / 55 (10.91%)	4 / 40 (10.00%)	
occurrences (all)	6	6	
Abdominal distension			
subjects affected / exposed	4 / 55 (7.27%)	5 / 40 (12.50%)	
occurrences (all)	4	5	
Haemorrhoids			
subjects affected / exposed	6 / 55 (10.91%)	2 / 40 (5.00%)	
occurrences (all)	10	6	
Abdominal pain lower			
subjects affected / exposed	3 / 55 (5.45%)	2 / 40 (5.00%)	
occurrences (all)	3	3	
Aphthous stomatitis			
subjects affected / exposed	4 / 55 (7.27%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Stomatitis			
subjects affected / exposed	3 / 55 (5.45%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	32 / 55 (58.18%)	20 / 40 (50.00%)	
occurrences (all)	32	21	
Pruritus			
subjects affected / exposed	3 / 55 (5.45%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Rash			
subjects affected / exposed	4 / 55 (7.27%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Dry skin			
subjects affected / exposed	2 / 55 (3.64%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	4 / 55 (7.27%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Urticaria			

subjects affected / exposed	1 / 55 (1.82%)	4 / 40 (10.00%)	
occurrences (all)	1	4	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 55 (7.27%)	4 / 40 (10.00%)	
occurrences (all)	5	5	
Proteinuria			
subjects affected / exposed	8 / 55 (14.55%)	2 / 40 (5.00%)	
occurrences (all)	9	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 55 (38.18%)	6 / 40 (15.00%)	
occurrences (all)	32	8	
Myalgia			
subjects affected / exposed	15 / 55 (27.27%)	9 / 40 (22.50%)	
occurrences (all)	25	12	
Back pain			
subjects affected / exposed	7 / 55 (12.73%)	3 / 40 (7.50%)	
occurrences (all)	7	3	
Muscle spasms			
subjects affected / exposed	6 / 55 (10.91%)	2 / 40 (5.00%)	
occurrences (all)	6	5	
Pain in extremity			
subjects affected / exposed	5 / 55 (9.09%)	3 / 40 (7.50%)	
occurrences (all)	6	4	
Musculoskeletal pain			
subjects affected / exposed	5 / 55 (9.09%)	2 / 40 (5.00%)	
occurrences (all)	5	2	
Neck pain			
subjects affected / exposed	4 / 55 (7.27%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	10 / 55 (18.18%)	5 / 40 (12.50%)	
occurrences (all)	13	9	
Nasopharyngitis			

subjects affected / exposed	7 / 55 (12.73%)	3 / 40 (7.50%)	
occurrences (all)	8	3	
Bronchitis			
subjects affected / exposed	6 / 55 (10.91%)	2 / 40 (5.00%)	
occurrences (all)	8	2	
Rhinitis			
subjects affected / exposed	2 / 55 (3.64%)	4 / 40 (10.00%)	
occurrences (all)	5	5	
Tooth abscess			
subjects affected / exposed	4 / 55 (7.27%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 55 (18.18%)	9 / 40 (22.50%)	
occurrences (all)	14	14	
Hypokalaemia			
subjects affected / exposed	5 / 55 (9.09%)	4 / 40 (10.00%)	
occurrences (all)	5	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2013	Added an exploratory objective in order to evaluate T cell repertory diversity and use immune repertoire diversity as a universal biomarker of immune status; Added an exclusion criterion (carcinosarcoma); Corrected the time points for tumor assessments, CA- 125 dosage, exploratory samples, and safety
18 April 2013	Added precisions about the schedule of assessments; Added collection of platelet count and liver function test at each visit.
07 August 2013	Updated the schedule of assessments and precision for assessment of creatinine clearance
14 March 2014	Removed blood RNA collection (exploratory objective); Added an independent review of photos aiming to evaluate extend of carcinomatosis after neoadjuvant therapy (exploratory objective)
01 October 2015	Updated the management of participants with any circulating tumor cells Grade 4 non-hematologic adverse event and the related method of analysis
08 February 2016	Updated the management of participants with any circulating tumor cells Grade 4 non-hematologic adverse event; Added a last follow-up visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported