Clinical trial results:
Open-label, multi-center, randomized, phase II study evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma

Summary

EudraCT number	2007-005017-19
Trial protocol	GB FR NL IT BE ES PL DE CZ Outside EU/EEA
Global end of trial date	30 April 2019

Results information

Result version number	v3 (current)
This version publication date	20 December 2019
First version publication date	07 August 2016
Version creation reason	• Correction of full data set Correction made to Subject number by country data.

Trial information

Trial identification

Sponsor protocol code	BO20924

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00643565
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland,
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000056-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

An open-label, multi-center, randomized, Phase 2 study designed to evaluate the benefit of the addition of bevacizumab to chemotherapy in participants presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 59
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Czech Republic: 2
Worldwide total number of subjects	154
EEA total number of subjects	148

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	6
Children (2-11 years)	77
Adolescents (12-17 years)	71
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma underwent screening assessments. An eligibility screening form was completed documenting the investigator's assessment of each screened participant with regard to inclusion and exclusion criteria. A screening failure log was maintained by the investigator.

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	Chemotherapy

Arm description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

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

Dosage and administration details:

Participants received ifosfamide at 3 grams per square meter (g/m^2) on Day 1 and Day 2 of each cycle for the first 9 cycles only.

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

Dosage and administration details:

Participants received vincristine at 1.5 milligrams per square meter (mg/m^2) (maximum single dose of 2 mg) every week for first 7 weeks and then on Day 1 of each cycle up to Cycle 9.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received actinomycin D at 1.5 mg/m^2 (maximum single dose of 2 mg) on Day 1 of each cycle for the first 9 cycles only.

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

Dosage and administration details:

Participants received doxorubicin at 30 mg/m^2 on Day 1 and Day 2 from Cycles 1 to 4 only.

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

Dosage and administration details:

Participants received vinorelbine at 25 mg/m^2 on Days 1, 8, and 15 of each cycle for 12 cycles of maintenance therapy phase.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received cyclophosphamide at 25 mg/m^2 every day for the entire duration of the cycle (i.e. 28 days).

Arm title	Bevacizumab + Chemotherapy

Arm description:

Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	RO4876646
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV infusion of bevacizumab at 7.5 mg/kg every 3 weeks in 3-week cycles for 9 cycles during induction treatment phase and at 5 mg/kg every 2 weeks in 4-weeks cycles for a total of 12 weeks.

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

Dosage and administration details:

Participants received ifosfamide at 3 g/m^2 on Day 1 and Day 2 of each cycle for the first 9 cycles only.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received vincristine at 1.5 mg/m^2 (maximum single dose of 2 mg) every week for first 7 weeks and then on Day 1 of each cycle up to Cycle 9.

Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received actinomycin D at 1.5 mg/m^2 (maximum single dose of 2 mg) on Day 1 of each cycle for the first 9 cycles only.

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

Dosage and administration details:

Participants received doxorubicin at 30 mg/m^2 on Day 1 and Day 2 from Cycles 1 to 4 only.

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

Dosage and administration details:

Participants received vinorelbine at 25 mg/m^2 on Days 1, 8, and 15 of each cycle for 12 cycles of maintenance therapy phase.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received cyclophosphamide at 25 mg/m^2 every day for the entire duration of the cycle (i.e. 28 days).

Number of subjects in period 1	Chemotherapy	Bevacizumab + Chemotherapy
Started	80	74
Completed	7	7
Not completed	73	67
Consent withdrawn by subject	4	1
Adverse event, non-fatal	5	8
Death	12	11
Refused Treat/Did Not Cooperate	-	1
Did Not Cooperate	-	1
Unknown	7	8

Progression Of Disease	18	14
Administrative/Other	22	16
Lost to follow-up	-	6
Recurrence Of Disease	2	1
Protocol deviation	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.	
Reporting group title	Bevacizumab + Chemotherapy
Reporting group description:	
Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.	

Reporting group values	Chemotherapy	Bevacizumab + Chemotherapy	Total
Number of subjects	80	74	154
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	6
Children (2-11 years)	39	38	77
Adolescents (12-17 years)	38	33	71
Age continuous Units: years			
arithmetic mean	10.5	10.3	
standard deviation	± 4.8	± 4.9	-
Gender categorical Units: Subjects			
Female	40	29	69
Male	40	45	85

End points

End points reporting groups

Reporting group title	Chemotherapy

Reporting group description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

Reporting group title	Bevacizumab + Chemotherapy

Reporting group description:

Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

Primary: Percentage of Participants Who Experienced Event-Free Survival (EFS) Events as Per Independent Review Committee (IRC) Assessment

End point title	Percentage of Participants Who Experienced Event-Free Survival (EFS) Events as Per Independent Review Committee (IRC) Assessment[1]

End point description:

EFS events included tumor progression (IRC assessed), no evidence of response after 3 cycles of induction (derived from IRC assessment), second primary cancer, or death due to any cause. Data for participants who had not experienced an event by the time of clinical cut-off were censored at the date of the last disease assessment prior to the clinical cut-off date. Data for participants who did not have any post-baseline disease assessments were censored at the time of randomization. Tumor progression was defined using Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0) as at least a 20 percent (%) increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or appearance of one or more new lesions, or evidence of clinical progression and unequivocal progression of existing non-target lesions. Intent-to-treat (ITT) population included all participants randomized to the treatment group in the study

End point type	Primary

End point timeframe:

Screening up to approximately 6.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years)

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: No statistical analysis was planned for this endpoint.

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	74		
Units: percentage of participants				
number (not applicable)	52.5	68.9		

Statistical analyses

No statistical analyses for this end point

Primary: EFS Duration as Per IRC Assessment

End point title	EFS Duration as Per IRC Assessment

End point description:

EFS was defined as the time between randomization and occurrence of EFS event (described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC"). Median EFS was estimated using Kaplan-Meier estimates and 95% confidence intervals (CI) for median was computed using the method of Brookmeyer and Crowley. ITT population.

End point type	Primary

End point timeframe:

Screening up to approximately 6.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years)

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	74		
Units: months				
median (confidence interval 95%)	14.85 (10.84 to 35.88)	20.63 (15.15 to 24.87)		

Statistical analyses

Statistical analysis title	EFS Duration as Per IRC Assessment
Comparison groups	Bevacizumab + Chemotherapy v Chemotherapy
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7189 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.41

Notes:

[2] - The HR was calculated based on a stratified Cox proportional hazards model, with stratification factors of age and histology/disease risk.

Secondary: Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria

End point title	Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria

End point description:

Objective response prior to first local therapy (surgery and/or radiotherapy) was defined as complete response (CR) or partial response (PR) determined on two consecutive occasions greater than equal to (>=) 4 weeks apart. Tumor response were assessed as per IRC using RECIST 1.0. CR was defined as disappearance of all target and non-target lesions. If immunocytology was available, no disease was to be detected by that methodology. PR was defined as at least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry. ITT population.

End point type	Secondary

End point timeframe:

Screening up to end approximately 6.75 years

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	74		
Units: percentage of participants				
number (confidence interval 95%)	36 (25.23 to 47.91)	54 (40.94 to 66.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced EFS Events Among Participants Who Had Objective Response

End point title	Percentage of Participants Who Experienced EFS Events Among Participants Who Had Objective Response

End point description:

EFS events was described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC" and in endpoint "Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria". ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Screening up to end approximately 6.75 years

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: percentage of participants				
number (not applicable)	40.7	76.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response was defined as the time between first objective response and the occurrence of an EFS event (described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC"). Objective response is defined in Outcome Measure “Percentage of Participants With Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria”. Median duration of response was estimated using Kaplan-Meier estimates and 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome measure. Here, “99.9” and “999.9”was used as median and upper limit of 95% CI, respectively, as data was not estimable because of higher number (more than 50%) of censored participants in this arm group.

End point type	Secondary

End point timeframe:

Screening up to end approximately 6.75 years

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: months				
median (confidence interval 95%)	99.9 (10.18 to 999.9)	17.48 (12.29 to 25.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

ITT population.

End point type	Secondary

End point timeframe:

Screening up to approximately 10.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years.

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	74		
Units: percentage of participants				
number (not applicable)	50	51.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Duration

End point title	Overall Survival Duration

End point description:

Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Median overall survival was estimated using Kaplan-Meier estimates and 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT population. Here number of participants analyzed = participants available for the analysis of this outcome measure. Here, "999" was used as upper limit of 95% CI, which was not estimable because of higher number (more than 50%) of censored participants in this arm group.

End point type	Secondary

End point timeframe:

Screening up to approximately 10.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years)

End point values	Chemotherapy	Bevacizumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	74		
Units: months				
median (confidence interval 95%)	24.02 (17.97 to 999)	32.79 (25.33 to 999)		

Statistical analyses

Statistical analysis title	Chemotherapy, Bevacizumab + Chemotherapy
Comparison groups	Chemotherapy v Bevacizumab + Chemotherapy

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3211 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.25

Notes:

[3] - The HR was calculated based on a stratified Cox proportional hazards model, with stratification factors of age and histology/disease risk.

Secondary: Area Under the Curve at Steady State (AUCss) of Bevacizumab

End point title	Area Under the Curve at Steady State (AUCss) of

End point description:

AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. AUCss is expressed in milligrams times days per milliliter (mg*day/mL). Pharmacokinetic (PK)-evaluable population included all randomized participants for whom at least one blood sample was taken for PK assessment following bevacizumab administration. Only participants who received bevacizumab were to be analyzed for PK assessment.

End point type	Secondary

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

End point values	Bevacizumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: mg*day/mL				
arithmetic mean (standard deviation)	1010 (± 256)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution of Bevacizumab

End point title	Volume of Distribution of Bevacizumab[5]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

End point type	Secondary

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

End point values	Bevacizumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: mL				
arithmetic mean (standard deviation)	2070 (± 891)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life of Bevacizumab

End point title	Half-Life of Bevacizumab[6]

End point description:

Half-life is the time measured for the plasma concentration to decrease by one half. PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

End point type	Secondary

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

End point values	Bevacizumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: days				
arithmetic mean (standard deviation)	20.8 (± 8.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of Bevacizumab

End point title	Clearance (CL) of Bevacizumab[7]

End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. CL is expressed in milliliters per day (mL/day). PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

End point type	Secondary

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

End point values	Bevacizumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: mL/day				
arithmetic mean (standard deviation)	167 (± 76.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to approximately 10.75 years	
Adverse event reporting additional description:	
The safety-evaluable population included all randomized participants who received any dose of study treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Chemotherapy
Reporting group description:	
Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Day 1 and 15 of 4-week cycles for a total of 12 cycles.	
Reporting group title	Bevacizumab + Chemotherapy
Reporting group description:	
Participants received continuous IV infusion of bevacizumab (7.5 mg/kg every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4 cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.	

Serious adverse events	Chemotherapy	Bevacizumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 79 (86.08%)	66 / 71 (92.96%)	
number of deaths (all causes)	40	37	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour necrosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 79 (1.27%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
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	7 / 79 (8.86%)	10 / 71 (14.08%)	
occurrences causally related to treatment / all	14 / 14	18 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	15 / 79 (18.99%)	14 / 71 (19.72%)	
occurrences causally related to treatment / all	19 / 26	3 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 79 (1.27%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			

subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida test positive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil toxic granulation present			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	3 / 79 (3.80%)	5 / 71 (7.04%)	
occurrences causally related to treatment / all	2 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haematoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torus fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recall phenomenon			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Fanconi syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiotoxicity			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 79 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 79 (2.53%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 79 (3.80%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	8 / 8	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	9 / 79 (11.39%)	19 / 71 (26.76%)	
occurrences causally related to treatment / all	24 / 24	49 / 49	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	47 / 79 (59.49%)	46 / 71 (64.79%)	
occurrences causally related to treatment / all	134 / 135	120 / 120	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 79 (3.80%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 79 (2.53%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 79 (3.80%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	3 / 79 (3.80%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	4 / 79 (5.06%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 79 (8.86%)	8 / 71 (11.27%)	
occurrences causally related to treatment / all	7 / 8	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			

subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin exfoliation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder necrosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 79 (5.06%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 79 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 79 (1.27%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	5 / 79 (6.33%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	4 / 8	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 79 (3.80%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 79 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	3 / 79 (3.80%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	4 / 4	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 79 (1.27%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 79 (2.53%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 79 (1.27%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemotherapy	Bevacizumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 79 (98.73%)	71 / 71 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 79 (3.80%)	4 / 71 (5.63%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 79 (12.66%)	17 / 71 (23.94%)	
occurrences (all)	12	23	
Chest pain			
subjects affected / exposed	6 / 79 (7.59%)	4 / 71 (5.63%)	
occurrences (all)	7	4	
Fatigue			
subjects affected / exposed	16 / 79 (20.25%)	18 / 71 (25.35%)	
occurrences (all)	27	26	
Mucosal inflammation			
subjects affected / exposed	38 / 79 (48.10%)	42 / 71 (59.15%)	
occurrences (all)	54	74	
Pain			
subjects affected / exposed	10 / 79 (12.66%)	5 / 71 (7.04%)	
occurrences (all)	11	6	
Pyrexia			
subjects affected / exposed	33 / 79 (41.77%)	27 / 71 (38.03%)	
occurrences (all)	73	46	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 79 (1.27%)	4 / 71 (5.63%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	13 / 79 (16.46%)	19 / 71 (26.76%)	
occurrences (all)	20	29	
Epistaxis			
subjects affected / exposed	8 / 79 (10.13%)	23 / 71 (32.39%)	
occurrences (all)	10	57	
Oropharyngeal pain			
subjects affected / exposed	7 / 79 (8.86%)	9 / 71 (12.68%)	
occurrences (all)	10	11	
Rhinorrhoea			
subjects affected / exposed	6 / 79 (7.59%)	4 / 71 (5.63%)	
occurrences (all)	6	7	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 79 (8.86%)	9 / 71 (12.68%)	
occurrences (all)	7	9	
Insomnia			
subjects affected / exposed	2 / 79 (2.53%)	5 / 71 (7.04%)	
occurrences (all)	2	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 79 (2.53%)	6 / 71 (8.45%)	
occurrences (all)	2	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 79 (3.80%)	4 / 71 (5.63%)	
occurrences (all)	3	5	
Haemoglobin decreased			
subjects affected / exposed	13 / 79 (16.46%)	7 / 71 (9.86%)	
occurrences (all)	27	18	
Neutrophil count decreased			
subjects affected / exposed	4 / 79 (5.06%)	3 / 71 (4.23%)	
occurrences (all)	7	15	
Platelet count decreased			
subjects affected / exposed	5 / 79 (6.33%)	4 / 71 (5.63%)	
occurrences (all)	13	13	
Weight decreased			

subjects affected / exposed	27 / 79 (34.18%)	22 / 71 (30.99%)	
occurrences (all)	31	26	
White blood cell count decreased			
subjects affected / exposed	2 / 79 (2.53%)	4 / 71 (5.63%)	
occurrences (all)	3	6	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 79 (1.27%)	7 / 71 (9.86%)	
occurrences (all)	1	8	
Radiation skin injury			
subjects affected / exposed	12 / 79 (15.19%)	8 / 71 (11.27%)	
occurrences (all)	12	9	
Radiation Injury			
subjects affected / exposed	1 / 79 (1.27%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	4 / 79 (5.06%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Tachycardia			
subjects affected / exposed	4 / 79 (5.06%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 79 (7.59%)	7 / 71 (9.86%)	
occurrences (all)	7	8	
Headache			
subjects affected / exposed	16 / 79 (20.25%)	32 / 71 (45.07%)	
occurrences (all)	23	49	
Neuralgia			
subjects affected / exposed	5 / 79 (6.33%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Neuropathy peripheral			
subjects affected / exposed	2 / 79 (2.53%)	9 / 71 (12.68%)	
occurrences (all)	2	10	
Paraesthesia			

subjects affected / exposed	3 / 79 (3.80%)	6 / 71 (8.45%)	
occurrences (all)	3	6	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 79 (2.53%)	5 / 71 (7.04%)	
occurrences (all)	3	6	
Polyneuropathy			
subjects affected / exposed	1 / 79 (1.27%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 79 (63.29%)	55 / 71 (77.46%)	
occurrences (all)	141	128	
Febrile neutropenia			
subjects affected / exposed	14 / 79 (17.72%)	12 / 71 (16.90%)	
occurrences (all)	23	16	
Leukopenia			
subjects affected / exposed	11 / 79 (13.92%)	13 / 71 (18.31%)	
occurrences (all)	30	36	
Neutropenia			
subjects affected / exposed	53 / 79 (67.09%)	56 / 71 (78.87%)	
occurrences (all)	244	264	
Thrombocytopenia			
subjects affected / exposed	37 / 79 (46.84%)	31 / 71 (43.66%)	
occurrences (all)	116	101	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	4 / 79 (5.06%)	5 / 71 (7.04%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 79 (34.18%)	31 / 71 (43.66%)	
occurrences (all)	43	58	
Abdominal pain upper			
subjects affected / exposed	8 / 79 (10.13%)	8 / 71 (11.27%)	
occurrences (all)	10	12	
Anal fissure			

subjects affected / exposed	5 / 79 (6.33%)	13 / 71 (18.31%)	
occurrences (all)	7	15	
Anal inflammation			
subjects affected / exposed	4 / 79 (5.06%)	6 / 71 (8.45%)	
occurrences (all)	7	7	
Constipation			
subjects affected / exposed	40 / 79 (50.63%)	48 / 71 (67.61%)	
occurrences (all)	61	95	
Diarrhoea			
subjects affected / exposed	27 / 79 (34.18%)	30 / 71 (42.25%)	
occurrences (all)	54	56	
Dyspepsia			
subjects affected / exposed	5 / 79 (6.33%)	4 / 71 (5.63%)	
occurrences (all)	5	4	
Mouth ulceration			
subjects affected / exposed	4 / 79 (5.06%)	3 / 71 (4.23%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	42 / 79 (53.16%)	44 / 71 (61.97%)	
occurrences (all)	146	145	
Oral pain			
subjects affected / exposed	4 / 79 (5.06%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Stomatitis			
subjects affected / exposed	23 / 79 (29.11%)	15 / 71 (21.13%)	
occurrences (all)	29	21	
Vomiting			
subjects affected / exposed	61 / 79 (77.22%)	64 / 71 (90.14%)	
occurrences (all)	186	202	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 79 (1.27%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	22 / 79 (27.85%)	17 / 71 (23.94%)	
occurrences (all)	23	18	
Dry skin			
subjects affected / exposed	2 / 79 (2.53%)	5 / 71 (7.04%)	
occurrences (all)	2	6	
Erythema			
subjects affected / exposed	6 / 79 (7.59%)	12 / 71 (16.90%)	
occurrences (all)	7	13	
Pruritus			
subjects affected / exposed	6 / 79 (7.59%)	10 / 71 (14.08%)	
occurrences (all)	7	14	
Rash			
subjects affected / exposed	10 / 79 (12.66%)	5 / 71 (7.04%)	
occurrences (all)	13	6	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 79 (3.80%)	7 / 71 (9.86%)	
occurrences (all)	3	10	
Haematuria			
subjects affected / exposed	2 / 79 (2.53%)	8 / 71 (11.27%)	
occurrences (all)	3	9	
Proteinuria			
subjects affected / exposed	4 / 79 (5.06%)	4 / 71 (5.63%)	
occurrences (all)	6	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 79 (10.13%)	10 / 71 (14.08%)	
occurrences (all)	10	15	
Back pain			
subjects affected / exposed	6 / 79 (7.59%)	15 / 71 (21.13%)	
occurrences (all)	8	23	
Bone pain			
subjects affected / exposed	2 / 79 (2.53%)	4 / 71 (5.63%)	
occurrences (all)	2	6	
Myalgia			

subjects affected / exposed	4 / 79 (5.06%)	6 / 71 (8.45%)	
occurrences (all)	4	9	
Pain in extremity			
subjects affected / exposed	16 / 79 (20.25%)	20 / 71 (28.17%)	
occurrences (all)	22	30	
Pain in jaw			
subjects affected / exposed	12 / 79 (15.19%)	5 / 71 (7.04%)	
occurrences (all)	14	5	
Infections and infestations			
Candida infection			
subjects affected / exposed	5 / 79 (6.33%)	0 / 71 (0.00%)	
occurrences (all)	5	0	
Conjunctivitis			
subjects affected / exposed	5 / 79 (6.33%)	7 / 71 (9.86%)	
occurrences (all)	5	7	
Ear infection			
subjects affected / exposed	3 / 79 (3.80%)	6 / 71 (8.45%)	
occurrences (all)	4	7	
Herpes zoster			
subjects affected / exposed	4 / 79 (5.06%)	3 / 71 (4.23%)	
occurrences (all)	4	3	
Infection			
subjects affected / exposed	3 / 79 (3.80%)	5 / 71 (7.04%)	
occurrences (all)	5	5	
Nasopharyngitis			
subjects affected / exposed	5 / 79 (6.33%)	10 / 71 (14.08%)	
occurrences (all)	8	15	
Oral candidiasis			
subjects affected / exposed	7 / 79 (8.86%)	5 / 71 (7.04%)	
occurrences (all)	11	7	
Paronychia			
subjects affected / exposed	0 / 79 (0.00%)	5 / 71 (7.04%)	
occurrences (all)	0	5	
Pharyngitis			
subjects affected / exposed	0 / 79 (0.00%)	4 / 71 (5.63%)	
occurrences (all)	0	5	

Rhinitis			
subjects affected / exposed	6 / 79 (7.59%)	12 / 71 (16.90%)	
occurrences (all)	7	20	
Upper respiratory tract infection			
subjects affected / exposed	7 / 79 (8.86%)	9 / 71 (12.68%)	
occurrences (all)	13	13	
Urinary tract infection			
subjects affected / exposed	2 / 79 (2.53%)	8 / 71 (11.27%)	
occurrences (all)	2	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 79 (22.78%)	21 / 71 (29.58%)	
occurrences (all)	21	27	
Hypokalaemia			
subjects affected / exposed	18 / 79 (22.78%)	8 / 71 (11.27%)	
occurrences (all)	20	9	
Hypomagnesaemia			
subjects affected / exposed	5 / 79 (6.33%)	2 / 71 (2.82%)	
occurrences (all)	5	2	
Hyponatraemia			
subjects affected / exposed	2 / 79 (2.53%)	4 / 71 (5.63%)	
occurrences (all)	2	4	
Hypophosphataemia			
subjects affected / exposed	4 / 79 (5.06%)	5 / 71 (7.04%)	
occurrences (all)	5	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2008	Amended inclusion criteria as related to assessment of cardiac function and related sections as to cardiac toxicity, documenting the stress-velocity index information on smaller age ranges (less than [<] 1 year, versus 1 to 2 years, 2 to 3 years, >3 years). In healthy children less than 3 years of age, the minimal shortening fraction documented was between 35% and 45%, compared to between 28% and 38% for children aged 3 years and older. Adequate cardiac function at screen was redefined as shortening fraction (SF) >=28% for participants of at least 3 years of age, and SF >=35% for participants below 3 years of age. The diagnosis of congestive heart failure was redefined to include a decrease of SF below 28% for participants of at least 3 years of age and below 35% for participants below 3 years of age, or if the SF decreased by an absolute of >=10 percentile points from the previous test. Dose modification guidelines for doxorubicin and bevacizumab in cases of treatment-emergent cardiotoxicity events were rewritten to included the redefinitions above.
22 January 2009	This amendment was done to describe study design and endpoints, radiological tumor assessment. Statistical analysis plan was amended to add the futility analysis which was performed on 80 participants who completed 6 cycles. Due to new requirements for safety follow-up after randomization that extended study duration by 4 years, and with the requirement that the events of the primary endpoint were to be assessed by magnetic resonance imaging and evaluated by a central independent image reviewing committee, the schedule of assessments and study procedures section were completely revised to provide clear guidance for treating physicians and to allow for a meaningful review of trial efficacy data. Amended the study population criteria.
30 May 2011	Updated with increased investigational site from 50 to 60. Updated with possibility of omission of the first two doses of bevacizumab (induction therapy Cycles 1 and 2) for participants who presented with a surgical wound, bone fracture, or bleeding related to tumor oozing not satisfactorily healed at randomization or transient clotting diathesis or transient obstructive renal failure that had not resolved at randomization. Updated randomization timeframe from 4 weeks to 3 weeks for participants who underwent a major surgical procedure or open biopsy, or had suffered from a significant traumatic injury or bone fracture prior to study entry.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported