



Clinical trial results:

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab, and Associated Biomarkers, in Combination With Paclitaxel Compared With Paclitaxel Plus Placebo as First-Line Treatment of Patients With HER2-Negative Metastatic Breast Cancer

Summary

EudraCT number	2011-005335-97
Trial protocol	DE BE GB IT BG
Global end of trial date	21 November 2017

Results information

Result version number	v1 (current)
This version publication date	02 December 2018
First version publication date	29 April 2016

Trial information

Trial identification

Sponsor protocol code	GO25632
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01663727
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	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)	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	21 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2014
Global end of trial reached?	Yes
Global end of trial date	21 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of bevacizumab + paclitaxel compared with placebo + paclitaxel as first-line treatment in participants with HER2-negative metastatic breast cancer (MBC) as measured by: - Progression-free survival (PFS) based on investigator tumor assessment in the intent-to-treat (ITT) participants population (co-primary endpoint). - PFS based on investigator tumor assessment in ITT participants with high baseline plasma VEGF-A levels (co-primary endpoint).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures. This study was conducted in accordance with GCP and investigators were trained according to applicable Sponsor Standard Operating Procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 August 2012
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	Argentina: 16
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 54
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Panama: 28
Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 104
Worldwide total number of subjects	481
EEA total number of subjects	115

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)	378
From 65 to 84 years	102
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 596 participants were screened of whom 115 were screen failures and 481 participants were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel+Placebo

Arm description:

Participants received paclitaxel 90 mg/m² IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

Arm type	Placebo
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:

The dose of paclitaxel was based on the participant's weight at each administration.

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

Dosage and administration details:

The placebo dose was based on the participant's most recent weight taken within 7 days of the first study drug dose (Cycle 1, Day 1) and remained the same throughout the study.

Arm title	Paclitaxel+ Bevacizumab
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Arm description:

Participants received paclitaxel 90 mg/m² IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

Arm type	Experimental
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:

The bevacizumab dose was based on the participant's most recent weight taken within 7 days of the first study drug dose (Cycle 1, Day 1) and remained the same

throughout the study.

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:

The dose of paclitaxel was based on the participant's weight at each administration.

Number of subjects in period 1	Paclitaxel+Placebo	Paclitaxel+Bevacizumab
Started	242	239
Completed	0	1
Not completed	242	238
Consent withdrawn by subject	18	25
Death	161	155
Withdrawal prior to dosing.	1	-
Participant Withdrawal and Adverse Event.	1	-
Study Terminated	51	50
Lost to follow-up	10	8

Baseline characteristics

Reporting groups

Reporting group title	Paclitaxel+Placebo
Reporting group description: Participants received paclitaxel 90 mg/m ² IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.	
Reporting group title	Paclitaxel+ Bevacizumab
Reporting group description: Participants received paclitaxel 90 mg/m ² IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.	

Reporting group values	Paclitaxel+Placebo	Paclitaxel+ Bevacizumab	Total
Number of subjects	242	239	481
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	196	182	378
From 65-84 years	46	56	102
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	54.7	55.8	
standard deviation	± 10.7	± 11.5	-
Sex: Female, Male Units: Subjects			
Female	237	236	473
Male	5	3	8

End points

End points reporting groups

Reporting group title	Paclitaxel+Placebo
Reporting group description: Participants received paclitaxel 90 mg/m ² IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.	
Reporting group title	Paclitaxel+ Bevacizumab
Reporting group description: Participants received paclitaxel 90 mg/m ² IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.	

Primary: Percentage of participants with Progression or death in Intent-to-Treat (ITT) Population

End point title	Percentage of participants with Progression or death in Intent-to-Treat (ITT) Population ^[1]
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End point description:

Tumor assessment was performed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by investigator. Disease progression was defined as at least 20 percent (%) increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 millimeter (mm), unequivocal progression of existing non-target lesions, or presence of new lesions. ITT population included all participants randomized to study treatment irrespective of whether the assigned treatment was actually received.

End point type	Primary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks)

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: The endpoint was qualitative in nature. Hence, no statistical analysis is provided.

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	239		
Units: percentage of participants				
number (not applicable)	69.4	63.6		

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival (PFS) in ITT Population

End point title	Progression free survival (PFS) in ITT Population
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End point description:

PFS was defined as the interval between the date of randomization and the first documentation of progressive disease or death from any cause. Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target

lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. PFS was estimated using Kaplan Meier method. ITT population included all participants randomized to study treatment irrespective of whether the assigned treatment was actually received.

End point type	Primary
End point timeframe:	
Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	239		
Units: months				
median (confidence interval 95%)	8.8 (7.4 to 9.3)	11.0 (9.5 to 12.2)		

Statistical analyses

Statistical analysis title	Paclitaxel+Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+ Bevacizumab v Paclitaxel+Placebo
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.51
upper limit	0.91

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Unstratified Analysis. Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab

Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.55
upper limit	0.97

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
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Statistical analysis description:

A stratified multivariate Cox regression model, including treatment, VEGF-A level, and interaction between treatment and VEGF-A level (low, high) as factors was used to estimate the interaction p-value of the treatment with VEGF-A level for PFS. Analysis for the interaction of treatment effect with the plasma VEGF-A levels was a secondary objective.

Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4619
Method	Wald Test

Primary: Percentage of participants with Progression or death in high baseline plasma vascular endothelial growth factor-A (VEGF-A) ITT population

End point title	Percentage of participants with Progression or death in high baseline plasma vascular endothelial growth factor-A (VEGF-A) ITT population ^[2]
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End point description:

Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. High baseline plasma VEGF-A ITT population: All participants randomized to study treatment with high baseline plasma VEGF-A levels (VEGF-A levels greater than or equal to 5.05 picograms per milliliter), irrespective of whether the assigned treatment was actually received.

End point type	Primary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

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: The endpoint was qualitative in nature. Hence, no statistical analysis is provided.

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (not applicable)	75.0	70.8		

Statistical analyses

No statistical analyses for this end point

Primary: PFS in high baseline plasma VEGF-A ITT population

End point title	PFS in high baseline plasma VEGF-A ITT population
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End point description:

PFS was defined as the interval between the date of randomization and the first documentation of progressive disease or death from any cause. Tumor assessment was performed as per RECIST v1.1 by investigator. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. PFS was estimated using Kaplan Meier method.

End point type	Primary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	120		
Units: months				
median (confidence interval 95%)	7.3 (5.6 to 8.7)	9.6 (9.0 to 11.0)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
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Statistical analysis description:

Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression.

Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
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Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	0.47
upper limit	0.88

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Unstratified analysis. Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	0.5
upper limit	0.93

Secondary: Percentage of Participants Who Died - ITT population	
End point title	Percentage of Participants Who Died - ITT population
End point description:	
End point type	Secondary
End point timeframe:	
From randomization till death or clinical cut-off (up to 244 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	239		
Units: percentage of participants				
number (not applicable)	64.9	64.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - ITT Population

End point title	Overall Survival (OS) - ITT Population
End point description:	
OS was defined as the interval between the date of randomization and death from any cause. OS was estimated using Kaplan Meier method. Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
From randomization till death or clinical cut-off (up to 244 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	239		
Units: months				
median (confidence interval 95%)	25.8 (21.8 to 30.2)	28.8 (22.8 to 32.8)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative).	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5877
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.18

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description: Unstratified analysis.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.21

Secondary: Percentage of Participants Who Died - High Baseline Plasma VEGF-A ITT Population

End point title	Percentage of Participants Who Died - High Baseline Plasma VEGF-A ITT Population
End point description: Analysis was performed on high baseline plasma VEGF-A ITT Population.	
End point type	Secondary
End point timeframe: From randomization till death or clinical cut-off (up to 244 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (not applicable)	74.2	71.1		

Statistical analyses

Secondary: OS - High Baseline Plasma VEGF-A ITT Population

End point title	OS - High Baseline Plasma VEGF-A ITT Population
End point description: OS was defined as the interval between the date of randomization and death from any cause. OS was estimated using Kaplan Meier method.	
End point type	Secondary
End point timeframe: From randomization till death or clinical cut-off (up to 244 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	120		
Units: months				
median (confidence interval 95%)	19.4 (16.5 to 25.0)	22.8 (18.2 to 31.6)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description: Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative).	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2745
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.14

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description: Unstratified analysis. Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3616
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.17

Secondary: Percentage of Participants With an Objective Response - ITT population

End point title	Percentage of Participants With an Objective Response - ITT population
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End point description:

Objective response was defined as having a Complete Response (CR) or Partial Response (PR) according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Measurable disease was defined by the presence of at least one measurable lesion by clinical measurement, chest x-ray, computed tomography (CT), or magnetic resonance imaging (MRI). Number of participants analyzed=participants from ITT population with measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 117.7 weeks)

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	202		
Units: percentage of participants				
number (confidence interval 95%)	33.2 (26.87 to 39.49)	54.0 (47.09 to 60.83)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher
Parameter estimate	Difference in Response Rates
Point estimate	20.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.45
upper limit	30.11

Secondary: Percentage of Participants With an Objective Response - High Baseline Plasma VEGF-A ITT Population

End point title	Percentage of Participants With an Objective Response - High Baseline Plasma VEGF-A ITT Population
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End point description:

Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Measurable disease was defined by the presence of at least one measurable lesion by clinical measurement, chest x-ray, CT, or MRI. Number of participants analyzed=participants from high baseline plasma VEGF-A ITT population with measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression, death or clinical cut-off (up to 111.3 weeks)

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	105		
Units: percentage of participants				
number (confidence interval 95%)	32.8 (24.22 to 41.30)	54.3 (44.76 to 63.81)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Fisher
Parameter estimate	Difference in Response Rates
Point estimate	21.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.73
upper limit	34.32

Secondary: Duration of Response - ITT Population

End point title	Duration of Response - ITT Population
End point description:	
Duration of response was defined as the time from the initial date of the objective response to documented disease progression or death (whichever occurred first). Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Disease progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. Analysis was performed using Kaplan Meier method.	
End point type	Secondary
End point timeframe:	
Baseline, every 8 weeks until documented disease progression or clinical cut-off (up to 117.7 weeks)	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	109		
Units: months				
median (confidence interval 95%)	9.2 (7.4 to 11.5)	9.5 (7.8 to 12.4)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Stratified analysis: Stratification factors were plasma VEGF-A level (low/high), prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative).	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2737
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.19

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Unstratified analysis. Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2959
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.19

Secondary: Duration of Response - High Baseline Plasma VEGF-A ITT Population

End point title	Duration of Response - High Baseline Plasma VEGF-A ITT Population
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End point description:

Duration of response was defined as the time from the initial date of the objective response to documented disease progression or death (whichever occurred first). Objective response was defined as having a CR or PR according to a RECIST criteria v 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. Disease progression was defined at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or presence of new lesions. Analysis was performed using Kaplan Meier method.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks until documented disease progression or clinical cut-off (up to 111.3 weeks)

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	57		
Units: months				
median (confidence interval 95%)	7.2 (5.6 to 9.5)	8.1 (7.1 to 11.1)		

Statistical analyses

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Stratified analysis: Stratification factors were prior adjuvant chemotherapy (yes/no) and estrogen receptor / progesterone receptor status (positive, negative). Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1783
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.18

Statistical analysis title	Paclitaxel+ Bevacizumab vs. Paclitaxel+Placebo
Statistical analysis description:	
Unstratified analysis. Hazards ratio was estimated by Cox regression.	
Comparison groups	Paclitaxel+Placebo v Paclitaxel+ Bevacizumab
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2429
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.22

Secondary: Percentage of Participants Who were Alive at 1 Year - ITT Population

End point title	Percentage of Participants Who were Alive at 1 Year - ITT Population
End point description:	
End point type	Secondary
End point timeframe:	
1 year	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	239		
Units: percentage of participants				
number (not applicable)	80.94	82.47		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Percentage of Participants Who were Alive at 1 Year - High Baseline Plasma VEGF-A ITT Population

End point title	Secondary: Percentage of Participants Who were Alive at 1 Year - High Baseline Plasma VEGF-A ITT Population
End point description:	
End point type	Secondary
End point timeframe:	
1 year	

End point values	Paclitaxel+Placebo	Paclitaxel+Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (not applicable)	69.27	80.96		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through 30 days after the last dose of study drug or clinical cut-off (up to 115.1 weeks)

Adverse event reporting additional description:

Safety population: All randomized participants who received at least one full or partial dose of any component of the study treatment (bevacizumab, placebo, or paclitaxel).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Paclitaxel+Placebo
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Reporting group description:

Participants received paclitaxel 90 mg/m² IV on Days 1, 8 and 15 and placebo matched to bevacizumab IV infusion on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

Reporting group title	Paclitaxel+ Bevacizumab
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Reporting group description:

Participants received paclitaxel 90 mg/m² IV on Days 1, 8 and 15 and bevacizumab IV 10 mg/kg on Days 1 and 15 of a 28 day cycle until progressive disease, treatment limiting toxicity or death.

Serious adverse events	Paclitaxel+Placebo	Paclitaxel+ Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 233 (19.31%)	66 / 238 (27.73%)	
number of deaths (all causes)	162	161	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 233 (0.86%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIAL THROMBOSIS			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CATHETER SITE ERYTHEMA			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
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			

Bronchospasm			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 233 (0.86%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 233 (0.86%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 233 (0.00%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 233 (0.86%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Urine output decreased			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Femoral neck fracture			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 233 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 233 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
STERNAL FRACTURE			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND DEHISCENCE			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 233 (0.43%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 233 (0.86%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 233 (0.43%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 233 (0.00%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic nerve disorder			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			

subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATARACT			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 233 (1.72%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 233 (0.43%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 233 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 233 (0.00%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 233 (1.29%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder pain			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 233 (0.00%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			

Pain of skin			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 233 (0.00%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			

subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 233 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 233 (0.00%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	2 / 233 (0.86%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 233 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 233 (1.29%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			

subjects affected / exposed	1 / 233 (0.43%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 233 (0.43%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			

subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE INFECTION			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA SEPSIS			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (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 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION BACTERIAL			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (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			
Decreased appetite			
subjects affected / exposed	2 / 233 (0.86%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 233 (0.43%)	0 / 238 (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	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			

subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LACTIC ACIDOSIS			
subjects affected / exposed	0 / 233 (0.00%)	1 / 238 (0.42%)	
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	Paclitaxel+Placebo	Paclitaxel+Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	225 / 233 (96.57%)	230 / 238 (96.64%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 233 (12.88%)	73 / 238 (30.67%)	
occurrences (all)	83	109	
Hot flush			
subjects affected / exposed	10 / 233 (4.29%)	15 / 238 (6.30%)	
occurrences (all)	30	17	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 233 (15.45%)	32 / 238 (13.45%)	
occurrences (all)	50	62	
Fatigue			
subjects affected / exposed	74 / 233 (31.76%)	88 / 238 (36.97%)	
occurrences (all)	123	156	
Pyrexia			
subjects affected / exposed	28 / 233 (12.02%)	34 / 238 (14.29%)	
occurrences (all)	37	59	
Oedema peripheral			
subjects affected / exposed	42 / 233 (18.03%)	41 / 238 (17.23%)	
occurrences (all)	57	56	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	30 / 233 (12.88%)	33 / 238 (13.87%)	
occurrences (all)	33	41	
Cough			
subjects affected / exposed	30 / 233 (12.88%)	43 / 238 (18.07%)	
occurrences (all)	38	59	
Epistaxis			
subjects affected / exposed	48 / 233 (20.60%)	97 / 238 (40.76%)	
occurrences (all)	77	158	
Dysphonia			
subjects affected / exposed	5 / 233 (2.15%)	19 / 238 (7.98%)	
occurrences (all)	5	24	
Oropharyngeal pain			
subjects affected / exposed	14 / 233 (6.01%)	18 / 238 (7.56%)	
occurrences (all)	15	23	
Rhinorrhoea			
subjects affected / exposed	3 / 233 (1.29%)	20 / 238 (8.40%)	
occurrences (all)	4	26	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 233 (6.44%)	8 / 238 (3.36%)	
occurrences (all)	15	8	
Insomnia			
subjects affected / exposed	20 / 233 (8.58%)	35 / 238 (14.71%)	
occurrences (all)	24	46	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 233 (6.87%)	21 / 238 (8.82%)	
occurrences (all)	19	32	
Alanine aminotransferase increased			
subjects affected / exposed	17 / 233 (7.30%)	21 / 238 (8.82%)	
occurrences (all)	21	37	
Neutrophil count decreased			
subjects affected / exposed	20 / 233 (8.58%)	15 / 238 (6.30%)	
occurrences (all)	100	56	
White blood cell count decreased			

subjects affected / exposed occurrences (all)	16 / 233 (6.87%) 84	21 / 238 (8.82%) 87	
WEIGHT DECREASED subjects affected / exposed occurrences (all)	5 / 233 (2.15%) 5	12 / 238 (5.04%) 13	
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	22 / 233 (9.44%) 24	33 / 238 (13.87%) 43	
Headache subjects affected / exposed occurrences (all)	44 / 233 (18.88%) 71	51 / 238 (21.43%) 85	
Dizziness subjects affected / exposed occurrences (all)	24 / 233 (10.30%) 25	28 / 238 (11.76%) 33	
Neuropathy peripheral subjects affected / exposed occurrences (all)	50 / 233 (21.46%) 67	47 / 238 (19.75%) 72	
Paraesthesia subjects affected / exposed occurrences (all)	17 / 233 (7.30%) 21	12 / 238 (5.04%) 14	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	84 / 233 (36.05%) 107	92 / 238 (38.66%) 129	
Blood and lymphatic system disorders			
Leukopenia subjects affected / exposed occurrences (all)	14 / 233 (6.01%) 42	17 / 238 (7.14%) 41	
Anaemia subjects affected / exposed occurrences (all)	39 / 233 (16.74%) 82	39 / 238 (16.39%) 63	
Neutropenia subjects affected / exposed occurrences (all)	50 / 233 (21.46%) 124	77 / 238 (32.35%) 254	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	17 / 233 (7.30%)	20 / 238 (8.40%)	
occurrences (all)	30	27	
Abdominal pain upper			
subjects affected / exposed	13 / 233 (5.58%)	13 / 238 (5.46%)	
occurrences (all)	14	16	
Diarrhoea			
subjects affected / exposed	72 / 233 (30.90%)	88 / 238 (36.97%)	
occurrences (all)	128	189	
Constipation			
subjects affected / exposed	50 / 233 (21.46%)	67 / 238 (28.15%)	
occurrences (all)	70	108	
Dyspepsia			
subjects affected / exposed	16 / 233 (6.87%)	23 / 238 (9.66%)	
occurrences (all)	20	40	
Toothache			
subjects affected / exposed	8 / 233 (3.43%)	15 / 238 (6.30%)	
occurrences (all)	9	16	
Nausea			
subjects affected / exposed	75 / 233 (32.19%)	99 / 238 (41.60%)	
occurrences (all)	205	310	
Stomatitis			
subjects affected / exposed	26 / 233 (11.16%)	42 / 238 (17.65%)	
occurrences (all)	35	75	
Vomiting			
subjects affected / exposed	36 / 233 (15.45%)	47 / 238 (19.75%)	
occurrences (all)	63	96	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	145 / 233 (62.23%)	140 / 238 (58.82%)	
occurrences (all)	159	149	
Nail discolouration			
subjects affected / exposed	18 / 233 (7.73%)	33 / 238 (13.87%)	
occurrences (all)	18	37	
Nail disorder			

subjects affected / exposed occurrences (all)	13 / 233 (5.58%) 13	13 / 238 (5.46%) 14	
Dry skin subjects affected / exposed occurrences (all)	7 / 233 (3.00%) 7	18 / 238 (7.56%) 20	
Onychomadesis subjects affected / exposed occurrences (all)	6 / 233 (2.58%) 6	15 / 238 (6.30%) 17	
Pruritis subjects affected / exposed occurrences (all)	10 / 233 (4.29%) 12	15 / 238 (6.30%) 17	
Rash subjects affected / exposed occurrences (all)	31 / 233 (13.30%) 36	58 / 238 (24.37%) 113	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	26 / 233 (11.16%) 33	32 / 238 (13.45%) 53	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	53 / 233 (22.75%) 86	53 / 238 (22.27%) 91	
Bone pain subjects affected / exposed occurrences (all)	20 / 233 (8.58%) 32	11 / 238 (4.62%) 17	
Pain in extremity subjects affected / exposed occurrences (all)	21 / 233 (9.01%) 23	23 / 238 (9.66%) 32	
Back pain subjects affected / exposed occurrences (all)	31 / 233 (13.30%) 42	26 / 238 (10.92%) 32	
Myalgia subjects affected / exposed occurrences (all)	28 / 233 (12.02%) 60	43 / 238 (18.07%) 83	
NECK PAIN			

subjects affected / exposed occurrences (all)	3 / 233 (1.29%) 5	12 / 238 (5.04%) 13	
MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all)	5 / 233 (2.15%) 8	12 / 238 (5.04%) 14	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	36 / 233 (15.45%) 65	24 / 238 (10.08%) 54	
Bronchitis subjects affected / exposed occurrences (all)	12 / 233 (5.15%) 12	11 / 238 (4.62%) 14	
Paronychia subjects affected / exposed occurrences (all)	7 / 233 (3.00%) 9	13 / 238 (5.46%) 13	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 233 (4.72%) 14	25 / 238 (10.50%) 26	
Urinary tract infection subjects affected / exposed occurrences (all)	16 / 233 (6.87%) 22	35 / 238 (14.71%) 47	
SINUSITIS subjects affected / exposed occurrences (all)	8 / 233 (3.43%) 12	12 / 238 (5.04%) 15	
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	10 / 233 (4.29%) 13	15 / 238 (6.30%) 22	
Decreased appetite subjects affected / exposed occurrences (all)	42 / 233 (18.03%) 65	55 / 238 (23.11%) 91	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2012	The protocol was amended to reflect the updated development plans for the VEGF-A assay. In Study GO25632, the IMPACT platform and assay was to be used to support participant enrollment while the new in vitro diagnostic (IVD) assay for clinical use was being developed and validated in parallel with the study. A bridging study was to be conducted to validate the newly developed IVD assay using the IMPACT measurements from Study BO17708 (AVADO) as a reference. - A list of possible VEGF-A testing sites was added in order to clarify which countries the samples might be sent to for VEGF-A testing. - To clarify treatment guidelines in that bevacizumab/placebo treatment could continue until disease progression in the event that paclitaxel was discontinued.
04 October 2012	To clarify regarding contraceptive use and the designation of paclitaxel as a study drug. Paclitaxel specific exclusion criteria to reflect IMP designation. Thus, depending on local classification, paclitaxel could either be considered a NIMP or an IMP. - A section was added on the addition of an IRF to demonstrate, through a sensitivity analysis, the robustness of the investigator-determined PFS according to RECIST. - Modifications were made to the internal monitoring committee (replaced by the iDMC), with details of the periodic review of unblinded safety data.
18 October 2013	The definition of the end of the study was amended to the date when 394 deaths in the ITT population have been observed. This follow-up OS analysis is expected to occur approximately 5.2 years after 326 progression-free survival events have occurred (i.e., approximately 6.5 years after the first participant was randomized). - An interaction test of treatment effect (PFS) with the VEGF-A level was included as a secondary endpoint. - Participants who were still receiving bevacizumab at the end of the study were to be offered participation in the Avastin Long-Term Extension study (AvaLTE. Protocol MO25757) if this study was approved in the participant's country. The objectives of Study MO25757 are to provide continued bevacizumab therapy as a single agent or in combination with an anti-cancer drug to participants with cancer who were previously enrolled in a bevacizumab study sponsored by F Hoffmann-La Roche Ltd. and Genentech Inc. and who derived benefit from the therapy administered.
14 September 2015	The protocol was amended to include an additional interim analysis for overall survival (OS) when the original projected number of events at the time of the primary progression free survival (PFS) analysis has been observed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported