Clinical trial results:
Randomized phase II trial of bevacizumab (AVASTIN®) in combination with gemcitabine or attenuated doses of cisplatin and gemcitabine as first-line treatment of elderly patients with advanced, metastatic nonsquamous non-small cell lung cancer

Summary

EudraCT number	2008-008739-27
Trial protocol	IT
Global end of trial date	02 July 2014

Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

Trial information

Trial identification

Sponsor protocol code	ML21868

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01077713
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of bevacizumab + gemcitabine combination and bevacizumab + cisplatin + gemcitabine combination in elderly participants with non-squamous NSCLC by using progression-free rate (PFR) at 6 months as primary endpoint.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	0
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 86 participants were enrolled and all of them were randomised.

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	Bevacizumab + Gemcitabine

Arm description:

Participants received bevacizumab 7.5 milligram per kilogram (mg/kg) intravenous (IV) infusion on Day 1 and gemcitabine 1200 milligrams per square meter (mg/m^2) IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg on IV infusion Day 1 of every 21-day cycle until progressive disease, death, or intolerable toxicity.

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

Dosage and administration details:

Bevacizumab (7.5 mg/kg) was administered as an IV infusion initially over a 90-minute period. If the first infusion was well tolerated, then the second infusion could be delivered over a 60-minute period. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over a 30-minute period.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1200 mg/m^2) was administered over a 30-minute IV infusion.

Arm title	Bevacizumab + Gemcitabine + Cisplatin

Arm description:

Participants received bevacizumab 7.5 mg/kg IV infusion and cisplatin 60 mg/m^2 IV infusion on Day 1 and gemcitabine 1000 mg/m^2 IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg IV infusion on Day 1 of every 21 day cycle until progressive disease, death, or intolerable toxicity.

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

Dosage and administration details:	
Bevacizumab (7 mg/kg) was administered as an IV infusion initially over a 90-minute period. If the first infusion was well tolerated, then the second infusion could be delivered over a 60-minute period. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over a 30-minute period.	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Gemcitabine (1200 mg/m^2) was administered over a 30-minute iv infusion.	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Cisplatin 60 (mg/m^2) was administered over a 1-hour IV infusion.	

Number of subjects in period 1	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin
Started	44	42
Completed	8	6
Not completed	36	36
Adverse event, serious fatal	28	29
Consent withdrawn by subject	1	2
Adverse event, non-fatal	2	1
Progressive Disease (PD)	-	1
Unspecified	4	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab + Gemcitabine
Reporting group description:	
Participants received bevacizumab 7.5 milligram per kilogram (mg/kg) intravenous (IV) infusion on Day 1 and gemcitabine 1200 milligrams per square meter (mg/m^2) IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg on IV infusion Day 1 of every 21-day cycle until progressive disease, death, or intolerable toxicity.	
Reporting group title	Bevacizumab + Gemcitabine + Cisplatin
Reporting group description:	
Participants received bevacizumab 7.5 mg/kg IV infusion and cisplatin 60 mg/m^2 IV infusion on Day 1 and gemcitabine 1000 mg/m^2 IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg IV infusion on Day 1 of every 21 day cycle until progressive disease, death, or intolerable toxicity.	

Reporting group values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin	Total
Number of subjects	44	42	86
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	74.2	73.8	
standard deviation	± 3.2	± 3.5	-
Gender, Male/Female Units: participants			
Female	16	12	28
Male	28	30	58

End points

End points reporting groups

Reporting group title	Bevacizumab + Gemcitabine

Reporting group description:

Participants received bevacizumab 7.5 milligram per kilogram (mg/kg) intravenous (IV) infusion on Day 1 and gemcitabine 1200 milligrams per square meter (mg/m^2) IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg on IV infusion Day 1 of every 21-day cycle until progressive disease, death, or intolerable toxicity.

Reporting group title	Bevacizumab + Gemcitabine + Cisplatin

Reporting group description:

Participants received bevacizumab 7.5 mg/kg IV infusion and cisplatin 60 mg/m^2 IV infusion on Day 1 and gemcitabine 1000 mg/m^2 IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg IV infusion on Day 1 of every 21 day cycle until progressive disease, death, or intolerable toxicity.

Primary: Percentage of participants alive and without progressive disease at Month 6

End point title	Percentage of participants alive and without progressive disease at Month 6[1]

End point description:

Disease progression was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1. 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 millimeter (mm), progression of existing non-target lesions, or presence of new lesions. All participants randomized set (RND) included all participants who provided informed consent and who were randomized to study medication. Intent-to-treat (ITT) set included all participants who provided informed consent and who were randomized to study medication who received at least one dose of any study medication; participants were classified according to treatment received.

End point type	Primary

End point timeframe:

Month 6

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: As this endpoint is descriptive in nature, no statistical analysis was performed.

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (confidence interval 95%)	25.6 (12.5 to 38.6)	30 (15.8 to 44.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Disease Progression or Death

End point title	Percentage of Participants with Disease Progression or Death

End point description:

Disease progression was assessed according to RECIST criteria version 1.1. 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, progression of existing non-target lesions, or presence of new lesions. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 15 of Cycles 3 and 6, and then every 3 months until disease progression, death, or consent withdrawal (up to 53 months)

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (not applicable)	86	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

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. Disease progression was assessed according to RECIST criteria version 1.1. 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, progression of existing non-target lesions, or presence of new lesions. PFS was estimated using Kaplan Meier method. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 15 of Cycles 3 and 6, and then every 3 months until disease progression, death or consent withdrawal (up to 53 months)

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: months				
median (confidence interval 95%)	4.33 (2.2 to 5.97)	6.82 (4.49 to 8.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive at 12 Months After Randomization

End point title	Percentage of Participants Alive at 12 Months After Randomization
End point description:	
Analysis was performed on ITT set.	
End point type	Secondary
End point timeframe:	
From randomization to one year	

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (confidence interval 95%)	37.2 (22.8 to 51.7)	47.5 (32 to 63)		

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:	
Analysis was performed on ITT set.	
End point type	Secondary
End point timeframe:	
From randomization to death or end of the study (up to 53 months)	

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (not applicable)	69.8	72.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

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 set.

End point type	Secondary

End point timeframe:

From randomization to death or end of the study (up to 53 months)

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: months				
median (confidence interval 95%)	5.66 (3.38 to 13)	12 (9.93 to 19.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Best Overall Response

End point title	Percentage of Participants by Best Overall Response

End point description:

Best overall response was defined as the best response recorded from the start of the treatment until disease progression/recurrence, assessed according to RECIST criteria version 1.1. Complete Response (CR): disappearance of all target and non-target lesions and no new lesions; Partial Response (PR): 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 lesion, and no new lesion; Progressive Disease (PD): 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, progression of existing non-target lesions, or presence of new lesions; Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 15 of Cycles 3 and 6, and then every 3 months until disease progression, death or consent withdrawal (up to 53 months)

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (not applicable)				
CR	0	0		
PR	14	35		
SD	39.5	37.5		
PD	16.3	12.5		
Not Assessable	30.2	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Response

End point title	Percentage of Participants with an Objective Response

End point description:

Objective response was defined as having a CR or PR according to a RECIST criteria version 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions. 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 lesion, and no new lesion. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Cycle 3 Day 15, Cycle 6 Day 15 and at Month 6

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 3	11.6 (2.05 to 21.2)	27.5 (13.7 to 41.3)		
Cycle 6	9.3 (0.62 to 18)	15 (3.93 to 26.1)		
Month 6	4.7 (0 to 10.9)	10 (0.7 to 19.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control

End point title	Percentage of Participants With Disease Control

End point description:

CR/PR/SD was measured by RECIST criteria version 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions. 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 lesion, and no new lesion. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD 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, progression of existing non-target lesions, or presence of new lesions. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Cycle 3 Day 15, Cycle 6 Day 15 and at Month 6

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 3	53.5 (38.6 to 68.4)	67.5 (53 to 82)		
Cycle 6	27.9 (14.5 to 41.3)	37.5 (22.5 to 52.5)		
Month 6	25.6 (12.5 to 38.6)	30 (15.8 to 44.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR was defined for participants who had achieved an objective response (CR/PR) (whichever status was recorded first) as the time period from 1st documentation of a response to the date of 1st occurrence of investigator documented disease progression or death. CR was defined as disappearance of all target and non-target lesions and no new lesions. 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 lesion, and no new lesion. Disease progression as increase by at least 20% in the sum of the longest diameters of each target lesion, taking as a reference the smallest sum of the longest diameters or appearance of one or more new lesions. DoR was estimated using Kaplan Meier method. Here "99999" represents data not available as tt was not possible to estimate statistic using Kaplan-Meier because upper bound of 95% confidence interval was not reached. Analysis was done on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Day 15 of Cycles 3 and 6, and then every 3 months until disease progression, death or consent withdrawal (up to 53 months)

End point values	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: months				
median (confidence interval 95%)	5.23 (3.93 to 99999)	5.97 (2.2 to 9.08)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to 28 days after last dose of any study drug (up to 54 months)

Adverse event reporting additional description:

Safety set included all participants in the RND set who received at least one dose of any study medication. Participants were classified according to treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Bevacizumab + Gemcitabine

Reporting group description:

Participants received bevacizumab 7.5 mg/kg IV infusion on Day 1 and gemcitabine 1200 mg/m^2 IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg on IV infusion Day 1 of every 21-day cycle until progressive disease, death, or intolerable toxicity.

Reporting group title	Bevacizumab + Gemcitabine + Cisplatin

Reporting group description:

Participants received bevacizumab 7.5 mg/kg IV infusion and cisplatin 60 mg/m^2 IV infusion on Day 1 and gemcitabine 1000 mg/m^2 IV infusion on Days 1-8 of each 21-day cycle for maximum of 6 cycles. After Cycle 6, participants continued treatment with bevacizumab 7.5 mg/kg IV infusion on Day 1 of every 21 day cycle until progressive disease, death, or intolerable toxicity.

Serious adverse events	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 43 (39.53%)	10 / 40 (25.00%)	
number of deaths (all causes)	30	29	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Embolism			
subjects affected / exposed	1 / 43 (2.33%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Artrial fibrillation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 43 (4.65%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 43 (4.65%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	2 / 43 (4.65%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 43 (4.65%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			

subjects affected / exposed	1 / 43 (2.33%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Bevacizumab + Gemcitabine	Bevacizumab + Gemcitabine + Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 43 (88.37%)	37 / 40 (92.50%)	
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 43 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	9	
Platelet count decreased			
subjects affected / exposed	4 / 43 (9.30%)	5 / 40 (12.50%)	
occurrences (all)	5	10	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 43 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	7	
Hypertension			
subjects affected / exposed	11 / 43 (25.58%)	9 / 40 (22.50%)	
occurrences (all)	16	12	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)	8 / 40 (20.00%)	
occurrences (all)	4	8	
Paraesthesia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 43 (11.63%)	12 / 40 (30.00%)	
occurrences (all)	7	34	
Leukopenia			

subjects affected / exposed	0 / 43 (0.00%)	11 / 40 (27.50%)	
occurrences (all)	0	39	
Neutropenia			
subjects affected / exposed	12 / 43 (27.91%)	23 / 40 (57.50%)	
occurrences (all)	27	60	
Thrombocytopenia			
subjects affected / exposed	5 / 43 (11.63%)	16 / 40 (40.00%)	
occurrences (all)	8	49	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 43 (20.93%)	10 / 40 (25.00%)	
occurrences (all)	11	17	
Chest pain			
subjects affected / exposed	4 / 43 (9.30%)	2 / 40 (5.00%)	
occurrences (all)	5	2	
Fatigue			
subjects affected / exposed	8 / 43 (18.60%)	15 / 40 (37.50%)	
occurrences (all)	10	34	
Mucosal inflammation			
subjects affected / exposed	0 / 43 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	7	
Pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	8 / 43 (18.60%)	8 / 40 (20.00%)	
occurrences (all)	13	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Constipation			

subjects affected / exposed	3 / 43 (6.98%)	8 / 40 (20.00%)	
occurrences (all)	3	8	
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)	5 / 40 (12.50%)	
occurrences (all)	3	8	
Nausea			
subjects affected / exposed	8 / 43 (18.60%)	17 / 40 (42.50%)	
occurrences (all)	12	36	
Vomiting			
subjects affected / exposed	5 / 43 (11.63%)	6 / 40 (15.00%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 43 (9.30%)	6 / 40 (15.00%)	
occurrences (all)	4	7	
Dyspnoea			
subjects affected / exposed	4 / 43 (9.30%)	7 / 40 (17.50%)	
occurrences (all)	4	7	
Epistaxis			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Haemoptysis			
subjects affected / exposed	5 / 43 (11.63%)	4 / 40 (10.00%)	
occurrences (all)	5	4	
Productive cough			
subjects affected / exposed	0 / 43 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 43 (11.63%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Bone pain			

subjects affected / exposed	5 / 43 (11.63%)	4 / 40 (10.00%)	
occurrences (all)	5	4	
Pain in extremity			
subjects affected / exposed	3 / 43 (6.98%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Tooth abscess			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	4	
Hypocalcaemia			
subjects affected / exposed	0 / 43 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	7	
Hyponatraemia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2010	The name of the sponsor Medical manager was changed; the exclusion criterion on radiotherapy was better clarified; specifications of end of treatment/study and of target population were better defined; the study schedule of assessments and the plan for follow-up were modified to meet the protocol definitions of adverse events reporting, and of clinical assessments and procedures; clarifications were given for the efficacy assessments; rules for the post-study provisional care were given; procedures for safety reporting and for reporting of adverse events of special interest were updated; the definition of the PP population for analysis was amended; procedures for central review of magnetic resonance imaging/computed tomography scan and for the data safety monitoring board were updated; procedures for publication of data have been updated; references for tumor assessment were updated in line with the adopted RECIST version 1.1 criteria.
27 September 2013	The name of the sponsor Medical manager was changed again; the definition for end of study was updated; the possibility of participation in the long-term extension study was offered to participants still on treatment with bevacizumab at end of study; the planned time for recruitment was extended; furthers specifications for the procedures of reporting of serious adverse events were added; the list of adverse events of special interest (and their definitions) was extended; clarifications for the efficacy and safety analysis were added; details on ethics and general study administration were added; the published reference for the ECOG performance status was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported