



Clinical trial results:

An Open-Label, Randomized, Phase IIIb Trial Evaluating the Efficacy and Safety of Standard of Care \pm Continuous Bevacizumab Treatment Beyond Progression of Disease in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) after First-Line Treatment with Bevacizumab plus a Platinum Doublet-Containing Chemotherapy

Summary

EudraCT number	2010-022645-14
Trial protocol	ES AT NL FR SK DK DE GR IT
Global end of trial date	24 June 2016

Results information

Result version number	v1 (current)
This version publication date	09 July 2017
First version publication date	09 July 2017

Trial information

Trial identification

Sponsor protocol code	MO22097
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01351415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
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	24 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy of continuous bevacizumab treatment beyond first progression of disease (PD) as measured by overall survival (OS)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2011
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: 12
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 112
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Greece: 28
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 26
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	United Arab Emirates: 3
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	485
EEA total number of subjects	348

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)	284
From 65 to 84 years	201
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This phase 3b study was conducted across 16 different countries and enrolled 485 subjects. Subjects were 18 years or older and had locally recurrent or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC)

Pre-assignment

Screening details:

A total of 485 subjects were enrolled and randomised into the study. Of these, 475 subjects were treated; 243 subjects received bevacizumab plus standard of care (SoC) and 232 subjects received SoC alone.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + Standard of Care

Arm description:

Subjects received bevacizumab on Day 1 of every 21-days cycle along with standard of care, until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

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:

Subjects received bevacizumab 7.5 milligram per kilogram (mg/kg) intravenously (i.v.) or 15 mg/kg i.v. on Day 1 every 21 days (± 3 days) from Cycle 1 until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurred first).

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Erlotinib 150 mg daily as SOC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

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

Dosage and administration details:

Subjects received Docetaxel 60 or 75 milligram per square meter (mg/m²) on Day 1 every 21 days (± 3 days) as 2nd-line SoC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

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

Dosage and administration details:

Subjects received Pemetrexed 500 mg/m² IV over 10 minutes on Day 1 every 21 days (±3 days) as 2nd-line SOC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

Arm title	Standard of Care
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Arm description:

Subjects received investigator's choice of standard of care (Erlotinib or Docetaxel or Pemetrexed) according to local practice until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Erlotinib 150 mg daily as SOC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

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

Dosage and administration details:

Subjects received Pemetrexed 500 mg/m² IV over 10 minutes on Day 1 every 21 days (±3 days) as 2nd-line SOC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

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

Dosage and administration details:

Subjects received Docetaxel 60 or 75 milligram per square meter (mg/m²) on Day 1 every 21 days (±3 days) as 2nd-line SoC treatment until the occurrence of unacceptable toxicity or withdrawal of consent (whichever occurred first)

Number of subjects in period 1	Bevacizumab + Standard of Care	Standard of Care
Started	245	240
Completed	0	0
Not completed	245	240
Adverse event, serious fatal	190	187

Consent withdrawn by subject	15	17
Physician decision	2	3
Never Started	5	5
Trial termination by the Sponsor	28	19
Reason unknown	-	2
Lost to follow-up	5	7

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab + Standard of Care
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Reporting group description:

Subjects received bevacizumab on Day 1 of every 21-days cycle along with standard of care, until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

Reporting group title	Standard of Care
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Reporting group description:

Subjects received investigator's choice of standard of care (Erlotinib or Docetaxel or Pemetrexed) according to local practice until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

Reporting group values	Bevacizumab + Standard of Care	Standard of Care	Total
Number of subjects	245	240	485
Age categorical Units: Subjects			

Age Continuous Units: Years arithmetic mean standard deviation	61.5 ± 9.61	61.8 ± 9.29	-
Gender, Male/Female Units: Subjects			
Female	90	102	192
Male	155	138	293

End points

End points reporting groups

Reporting group title	Bevacizumab + Standard of Care
Reporting group description: Subjects received bevacizumab on Day 1 of every 21-days cycle along with standard of care, until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).	
Reporting group title	Standard of Care
Reporting group description: Subjects received investigator's choice of standard of care (Erlotinib or Docetaxel or Pemetrexed) according to local practice until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: Overall survival (OS) was defined as the time from the date of randomisation at first progression of disease to the date of death, regardless of the cause of death. Intent to treat population included all randomised subjects.	
End point type	Primary
End point timeframe: Up to data cut-off date 24 June 2016 (approximately 5 years)	

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Months				
median (confidence interval 90%)	11.86 (10.22 to 13.67)	10.22 (8.61 to 11.93)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Statistical analysis description: The stratification factors for Log-Rank test and Hazard Ratio (HR) are the type of planned 2nd-line SoC treatment, the number of cycles of bevacizumab maintenance treatment prior to first PD and smoking status.	
Comparison groups	Bevacizumab + Standard of Care v Standard of Care

Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1044
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.71
upper limit	1

Secondary: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
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End point description:

PFS was defined as the time from start of treatment to the first event of death or PD. Tumor response was assessed by the IRF according to RECIST v1.1. Progression of disease (PD) was defined as $\geq 20\%$ increase in sum longest diameter (LD) in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. PFS2 is defined as the time between randomisation at PD1 and the date of PD2 or death, whichever occurs first. PFS3 is defined as the time between PD2 and the date of PD3 or death, whichever occurs first. Intent to treat population included all randomised subjects.

End point type	Secondary
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End point timeframe:

Up to data cut-off date 24 June 2016 (approximately 5 years)

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Months				
median (confidence interval 90%)				
PFS 2	5.45 (4.21 to 5.68)	3.98 (3.38 to 4.3)		
PFS 3	4.01 (2.86 to 4.47)	2.6 (2.33 to 2.92)		

Statistical analyses

Statistical analysis title	PFS2
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Statistical analysis description:

PFS2: The stratification factors for Log-Rank test are the type of planned 2nd-line SoC treatment, the number of cycles of bevacizumab maintenance treatment prior to PD1 and the smoking status.

Comparison groups	Bevacizumab + Standard of Care v Standard of Care
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Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0573
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	0.98

Statistical analysis title	PFS3
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Statistical analysis description:

PFS3: The stratification factors for Log Rank test and Hazard Ratio (HR) are the type of planned 2nd-line SOC treatment, the number of cycles of bevacizumab maintenance treatment prior to first PD and smoking status.

Comparison groups	Bevacizumab + Standard of Care v Standard of Care
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0045
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.49
upper limit	0.83

Secondary: Percentage of Subjects with Objective Response According to RECIST v1.1

End point title	Percentage of Subjects with Objective Response According to RECIST v1.1
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End point description:

The objective response is defined as complete response (CR) or partial response (PR) assessed according to the RECIST v.1.1 criteria with baseline tumour assessment as the reference. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumour marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined ≥ 30 percent (%) decrease in sum of longest diameter of target lesions in reference to Baseline sum longest diameter. Response was to be confirmed ≥ 4 weeks after the initial assessment of CR or PR. Intent to treat population included all randomised subjects.

End point type	Secondary
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End point timeframe:

Up to data cut-off date 24 June 2016 (approximately 5 years)

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Percentage of Subjects				
number (confidence interval 90%)	8.6 (5.86 to 12.21)	6.3 (3.91 to 9.5)		

Statistical analyses

Statistical analysis title	Objective Response
Statistical analysis description:	
The stratification factors for Cochran-Mantel-Haenszel test are the type of planned 2nd-line SoC treatment, the number of cycles of Bevacizumab maintenance treatment prior to PD1 and the smoking status.	
Comparison groups	Bevacizumab + Standard of Care v Standard of Care
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.081
Method	Stratified Cochran-Mantel-Haenszel test
Parameter estimate	Estimated difference in response rate
Point estimate	0.0237
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0156
upper limit	0.063

Secondary: Percentage of Subjects With Disease Control According to RECIST v1.1

End point title	Percentage of Subjects With Disease Control According to RECIST v1.1
End point description:	
The disease control rate is defined as CR or PR or stable disease (SD) assessed according to the RECIST v.1.1 criteria with baseline tumour assessment as the reference. SD was defined as neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since treatment started for target lesions and the persistence of 1 or more non-target lesions. Intent to treat population included all randomised subjects.	
End point type	Secondary
End point timeframe:	
Up to data cut-off date 24 June 2016 (approximately 5 years)	

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Percentage of Subjects				
number (confidence interval 90%)	80.2 (75.57 to 84.36)	77 (72.06 to 81.41)		

Statistical analyses

Statistical analysis title	Disease Control Rate
Statistical analysis description:	
The stratification factors for Cochran-Mantel-Haenszel test are the type of planned 2nd-line SoC treatment, the number of cycles of Bevacizumab maintenance treatment prior to PD1 and the smoking status.	
Comparison groups	Bevacizumab + Standard of Care v Standard of Care
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0218
Method	Stratified Cochran-Mantel-Haenszel test
Parameter estimate	Estimated difference in Disease Control
Point estimate	0.0326
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0288
upper limit	0.094

Secondary: Duration of Response (DoR) According to RECIST v1.1

End point title	Duration of Response (DoR) According to RECIST v1.1
End point description:	
DOR is defined as the time that measurement criteria are met for objective response (CR/PR) (whichever status is recorded first) until the first date of progression or death is documented. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumour marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than < 10 mm. PR was defined as greater than or equal to ≥30 % decrease in sum of longest diameter of target lesions in reference to baseline sum longest diameter. Intent to treat population included all randomised subjects.	
End point type	Secondary
End point timeframe:	
Up to data cut-off date 24 June 2016 (approximately 5 years)	

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Months				
median (confidence interval 90%)	7.46 (5.39 to 8.54)	6.24 (3.52 to 6.83)		

Statistical analyses

Statistical analysis title	DOR
Statistical analysis description:	
The stratification factors for Log-Rank test are the type of planned 2nd-line SoC treatment, the number of cycles of Bevacizumab maintenance treatment prior to PD1 and the smoking status.	
Comparison groups	Bevacizumab + Standard of Care v Standard of Care
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.09
upper limit	0.9

Secondary: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)
End point description:	
An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study and laboratory or clinical tests that resulted in a change in treatment or discontinuation from study drug were reported as adverse events. A SAE was any experience that: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was medically significant. The safety population included all subjects who had received at least one dose of any study drug.	
End point type	Secondary
End point timeframe:	
Up to data cut-off date 24 June 2016 (approximately 5 years)	

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	232		
Units: Percentage of Subjects				
number (not applicable)				
AEs	97.5	96.1		
SAEs	51.9	37.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) According to RECIST v1.1

End point title	Time to Progression (TTP) According to RECIST v1.1
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End point description:

The time to progression was defined as the time from baseline until disease progression as determined by the RECIST v1.1. TTP2 is defined as the interval between the day of randomization at PD1 and PD2. TTP3 is defined as the interval between the day of PD2 and PD3. PD was defined as $\geq 20\%$ increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Intent to treat population included all randomised subjects.

End point type	Secondary
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End point timeframe:

Up to data cut-off date 24 June 2016 (approximately 5 years)

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Months				
median (confidence interval 90%)				
TTP2	5.55 (4.86 to 6.18)	4.21 (3.75 to 5.06)		
TTP3	4.07 (3.25 to 4.63)	2.73 (2.37 to 3.06)		

Statistical analyses

Statistical analysis title	TTP2
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Statistical analysis description:

TTP2: The stratification factors for Log-Rank test are the type of planned 2nd-line SoC treatment, the number of cycles of Bevacizumab maintenance treatment prior to PD1 and the smoking status.

Comparison groups	Bevacizumab + Standard of Care v Standard of Care
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Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0311
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Statistical analysis title	TTP3
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Statistical analysis description:

TTP3: The stratification factors for Log-Rank test are the type of planned 2nd-line SoC treatment, the number of cycles of Bevacizumab maintenance treatment prior to PD1 and the smoking status.

Comparison groups	Bevacizumab + Standard of Care v Standard of Care
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0326
Method	Stratified Log-Rank test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	0.92

Secondary: Percentage of Subjects Who Are Alive at Month 6, 12, and 18

End point title	Percentage of Subjects Who Are Alive at Month 6, 12, and 18
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End point description:

Percentage of subjects who were alive at Month 6, 12 and 18 were reported. Intent to treat population included all randomised subjects.

End point type	Secondary
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End point timeframe:

Month 6, 12, 18

End point values	Bevacizumab + Standard of Care	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	240		
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 6	0.8 (0.73 to 0.82)	0.7 (0.62 to 0.72)		
Month 12	0.5 (0.44 to 0.54)	0.4 (0.39 to 0.5)		
Month 18	0.4 (0.31 to 0.41)	0.3 (0.25 to 0.36)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to data cut-off date 24 June 2016 (approximately 5 years)

Adverse event reporting additional description:

The safety population included all subjects who had received at least one dose of any study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Standard of Care
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Reporting group description:

Subjects received investigator's choice of standard of care (Erlotinib or Docetaxel or Pemetrexed) according to local practice until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

Reporting group title	Bevacizumab + Standard of Care
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Reporting group description:

Subjects received bevacizumab on Day 1 of every 21-days cycle along with standard of care (Erlotinib or Docetaxel or Pemetrexed) as second line treatment, until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first).

Serious adverse events	Standard of Care	Bevacizumab + Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 232 (37.07%)	126 / 243 (51.85%)	
number of deaths (all causes)	193	194	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to Adrenals			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Embolism			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Osteosynthesis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 232 (0.00%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 232 (0.86%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	2 / 232 (0.86%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General Physical Health Deterioration			
subjects affected / exposed	2 / 232 (0.86%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	1 / 232 (0.43%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance Status Decreased			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 232 (0.43%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Uterine Haemorrhage			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute Respiratory Failure			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Disorder			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 232 (0.00%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (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	3 / 232 (1.29%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 232 (0.86%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	2 / 232 (0.86%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	3 / 232 (1.29%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organizing Pneumonia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	4 / 232 (1.72%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			

subjects affected / exposed	6 / 232 (2.59%)	5 / 243 (2.06%)	
occurrences causally related to treatment / all	0 / 6	5 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Thrombosis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State			
subjects affected / exposed	2 / 232 (0.86%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	0 / 232 (0.00%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Increased			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Alcohol Poisoning			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial Injury			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Limb Fracture			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheo-oesophageal Fistula			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 232 (0.43%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac Failure			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral Ischaemia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (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	1 / 232 (0.43%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior Reversible Encephalopathy Syndrome			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 232 (2.59%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Failure			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Bone Marrow Aplasia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	9 / 232 (3.88%)	12 / 243 (4.94%)	
occurrences causally related to treatment / all	0 / 9	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	6 / 232 (2.59%)	9 / 243 (3.70%)	
occurrences causally related to treatment / all	0 / 7	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 232 (0.86%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pure White Cell Aplasia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 232 (0.86%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 232 (0.86%)	7 / 243 (2.88%)	
occurrences causally related to treatment / all	0 / 2	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Obstruction			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia Strangulated			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large Intestine Perforation			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mechanical Ileus			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Stenosis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis Intestinalis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Perforation			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 232 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Obstruction			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Stone			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Disorder			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema Multiforme			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Toxicity			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic Syndrome			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Prerenal Failure			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Tubular Disorder			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone Pain			
subjects affected / exposed	2 / 232 (0.86%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervetebral Disc Protrusion			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 232 (0.86%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	2 / 232 (0.86%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal Abcess			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis Perforated			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related Infection			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea Infectious			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Infection			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital Herpes Simplex			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Abscess			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 232 (0.43%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Periorbital Abscess			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	19 / 232 (8.19%)	13 / 243 (5.35%)	
occurrences causally related to treatment / all	0 / 22	2 / 13	
deaths causally related to treatment / all	0 / 8	0 / 2	
Post Procedural Infection			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas Abscess			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 232 (0.43%)	6 / 243 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract Infection Bacterial			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 232 (0.00%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Abscess			

subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
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 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 232 (0.43%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 232 (0.86%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 232 (0.43%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 232 (0.86%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetany			
subjects affected / exposed	0 / 232 (0.00%)	1 / 243 (0.41%)	
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	Standard of Care	Bevacizumab + Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 232 (92.67%)	226 / 243 (93.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 232 (10.78%)	52 / 243 (21.40%)	
occurrences (all)	36	97	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	61 / 232 (26.29%)	68 / 243 (27.98%)	
occurrences (all)	123	169	
Fatigue			
subjects affected / exposed	73 / 232 (31.47%)	71 / 243 (29.22%)	
occurrences (all)	113	144	
Malaise			
subjects affected / exposed	14 / 232 (6.03%)	24 / 243 (9.88%)	
occurrences (all)	26	32	
Chest Pain			
subjects affected / exposed	16 / 232 (6.90%)	26 / 243 (10.70%)	
occurrences (all)	22	37	
Mucosal Inflammation			
subjects affected / exposed	22 / 232 (9.48%)	49 / 243 (20.16%)	
occurrences (all)	28	79	
Oedema Peripheral			

subjects affected / exposed occurrences (all)	32 / 232 (13.79%) 41	34 / 243 (13.99%) 42	
Pain subjects affected / exposed occurrences (all)	13 / 232 (5.60%) 18	10 / 243 (4.12%) 11	
Pyrexia subjects affected / exposed occurrences (all)	35 / 232 (15.09%) 54	46 / 243 (18.93%) 76	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	56 / 232 (24.14%) 74	56 / 243 (23.05%) 95	
Dysphonia subjects affected / exposed occurrences (all)	13 / 232 (5.60%) 14	13 / 243 (5.35%) 14	
Cough subjects affected / exposed occurrences (all)	40 / 232 (17.24%) 51	39 / 243 (16.05%) 53	
Epistaxis subjects affected / exposed occurrences (all)	20 / 232 (8.62%) 22	53 / 243 (21.81%) 70	
Haemoptysis subjects affected / exposed occurrences (all)	11 / 232 (4.74%) 13	17 / 243 (7.00%) 18	
Pleural Effusion subjects affected / exposed occurrences (all)	15 / 232 (6.47%) 15	13 / 243 (5.35%) 25	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	15 / 232 (6.47%) 15	14 / 243 (5.76%) 14	
Anxiety subjects affected / exposed occurrences (all)	12 / 232 (5.17%) 13	11 / 243 (4.53%) 11	
Investigations			

Blood Creatinine Increased subjects affected / exposed occurrences (all)	4 / 232 (1.72%) 6	13 / 243 (5.35%) 21	
Weight Decreased subjects affected / exposed occurrences (all)	24 / 232 (10.34%) 35	42 / 243 (17.28%) 46	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	13 / 232 (5.60%) 14	20 / 243 (8.23%) 28	
Paraesthesia subjects affected / exposed occurrences (all)	8 / 232 (3.45%) 11	15 / 243 (6.17%) 32	
Neuropathy Peripheral subjects affected / exposed occurrences (all)	16 / 232 (6.90%) 21	20 / 243 (8.23%) 28	
Dysgeusia subjects affected / exposed occurrences (all)	16 / 232 (6.90%) 19	29 / 243 (11.93%) 32	
Headache subjects affected / exposed occurrences (all)	23 / 232 (9.91%) 27	39 / 243 (16.05%) 56	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	69 / 232 (29.74%) 129	54 / 243 (22.22%) 120	
Neutropenia subjects affected / exposed occurrences (all)	20 / 232 (8.62%) 47	39 / 243 (16.05%) 78	
Leukopenia subjects affected / exposed occurrences (all)	10 / 232 (4.31%) 22	16 / 243 (6.58%) 31	
Thrombocytopenia subjects affected / exposed occurrences (all)	9 / 232 (3.88%) 18	15 / 243 (6.17%) 27	
Eye disorders			

Lacrimation Increased subjects affected / exposed occurrences (all)	12 / 232 (5.17%) 13	18 / 243 (7.41%) 20	
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	13 / 232 (5.60%) 15	16 / 243 (6.58%) 22	
Constipation subjects affected / exposed occurrences (all)	49 / 232 (21.12%) 71	64 / 243 (26.34%) 94	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	14 / 232 (6.03%) 14	25 / 243 (10.29%) 33	
Diarrhoea subjects affected / exposed occurrences (all)	72 / 232 (31.03%) 112	90 / 243 (37.04%) 156	
Nausea subjects affected / exposed occurrences (all)	61 / 232 (26.29%) 98	84 / 243 (34.57%) 184	
Vomiting subjects affected / exposed occurrences (all)	40 / 232 (17.24%) 50	51 / 243 (20.99%) 70	
Stomatitis subjects affected / exposed occurrences (all)	26 / 232 (11.21%) 47	39 / 243 (16.05%) 72	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	41 / 232 (17.67%) 45	55 / 243 (22.63%) 66	
Dermatitis Acneiform subjects affected / exposed occurrences (all)	8 / 232 (3.45%) 13	15 / 243 (6.17%) 43	
Dry Skin subjects affected / exposed occurrences (all)	22 / 232 (9.48%) 26	29 / 243 (11.93%) 35	
Erythema			

subjects affected / exposed	17 / 232 (7.33%)	11 / 243 (4.53%)	
occurrences (all)	21	14	
Rash			
subjects affected / exposed	46 / 232 (19.83%)	49 / 243 (20.16%)	
occurrences (all)	58	76	
Pruritus			
subjects affected / exposed	14 / 232 (6.03%)	17 / 243 (7.00%)	
occurrences (all)	16	20	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	23 / 232 (9.91%)	51 / 243 (20.99%)	
occurrences (all)	40	125	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 232 (9.05%)	21 / 243 (8.64%)	
occurrences (all)	31	24	
Back Pain			
subjects affected / exposed	31 / 232 (13.36%)	28 / 243 (11.52%)	
occurrences (all)	37	34	
Musculoskeletal Chest Pain			
subjects affected / exposed	8 / 232 (3.45%)	13 / 243 (5.35%)	
occurrences (all)	10	13	
Musculoskeletal Pain			
subjects affected / exposed	18 / 232 (7.76%)	22 / 243 (9.05%)	
occurrences (all)	20	30	
Pain in Extremity			
subjects affected / exposed	16 / 232 (6.90%)	17 / 243 (7.00%)	
occurrences (all)	17	22	
Myalgia			
subjects affected / exposed	18 / 232 (7.76%)	18 / 243 (7.41%)	
occurrences (all)	21	50	
Infections and infestations			
Pneumonia			
subjects affected / exposed	12 / 232 (5.17%)	9 / 243 (3.70%)	
occurrences (all)	15	12	
Conjunctivitis			

subjects affected / exposed occurrences (all)	13 / 232 (5.60%) 19	16 / 243 (6.58%) 47	
Bronchitis subjects affected / exposed occurrences (all)	12 / 232 (5.17%) 14	23 / 243 (9.47%) 23	
Urinary Tract Infection subjects affected / exposed occurrences (all)	10 / 232 (4.31%) 11	16 / 243 (6.58%) 27	
Respiratory Tract Infection subjects affected / exposed occurrences (all)	9 / 232 (3.88%) 9	13 / 243 (5.35%) 16	
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	59 / 232 (25.43%) 81	83 / 243 (34.16%) 160	
Dehydration subjects affected / exposed occurrences (all)	2 / 232 (0.86%) 2	13 / 243 (5.35%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2011	<p>Archival tissue sample collection was added as current data on bevacizumab biomarker are inconclusive and more data were needed to better target therapies for subjects.</p> <p>Guidance on further treatment for subject with a complete response (CR) was added.</p> <p>Guidance on dose modification of bevacizumab according to weight changes was added as SOC at many participating sites was to use the "current" weight to calculate doses.</p> <p>The guidance for management of Grade 3 or Grade 4 bevacizumab-related AEs and management of hypertension was updated, in line with the updated bevacizumab Roche protocol template.</p>
02 July 2013	<p>It was clarified the approved (per label) dose of bevacizumab (7.5 or 15 mg/kg i.v.) used during the 1st-line treatment was to be the same dose administered to each patient during the study. It was also clarified the same Q3W schedule was also to be used; this also applied to the SoC agents used as part of 2nd-line treatment.</p> <p>The 21-day cycle requirement for SoC agents was removed as this was based on local practice. Bevacizumab was to continue to be administered on a 21-day cycle. The definition of treatment interruptions was updated.</p> <p>No safety concerns regarding the use of radiotherapy with bevacizumab were raised from previous studies or the current study. Therefore, amendments were made to exclusion criteria and to conditions if palliative radiotherapy to the brain was given during the study.</p> <p>To comply with new European Union Pharmacovigilance regulations, the reporting requirements for serious AEs (SAEs) and selected adverse events of special interest (AESIs) were revised from within "one working day" to within "24 hours after learning of the event". The recruitment period was extended from approximately 24 months to approximately 45 months. The number of sites was increased from 140 sites to approximately 160 sites.</p>
18 August 2014	<p>The total number of subjects to be recruited was reduced from 600 to approximately 500 subjects.</p> <p>The end of study was redefined to occur once 416 deaths had been observed (originally 519 deaths) or at 60 months from study start, whichever occurred first. Study design assumptions and properties for the comparison of the primary outcome (median OS beyond progression) were revised due to decreased planned sample size.</p> <p>An interim efficacy analysis was planned to occur after 70% of the OS events had been observed. In order to optimize the primary analysis, this interim analysis was no longer planned.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported