



Clinical trial results:

Global Study to Assess the Addition of Bevacizumab to Carboplatin and Paclitaxel as Front Line Treatment of Epithelial Ovarian Cancer, Fallopian Tube Carcinoma or Primary Peritoneal Carcinoma

Summary

EudraCT number	2010-019525-34
Trial protocol	SK FR ES LT AT LV NL IE SE EE HU IT BG DK SI GR PT PL
Global end of trial date	18 March 2015

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

Trial information

Trial identification

Sponsor protocol code	MO22923
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01239732
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	07 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety profile of bevacizumab when added to carboplatin and paclitaxel chemotherapy as front-line treatment of epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma.

Protection of trial subjects:

The study was conducted in accordance with the principles of the 'Declaration of Helsinki' and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2010
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: 7
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Egypt: 10
Country: Number of subjects enrolled	Estonia: 15
Country: Number of subjects enrolled	France: 97
Country: Number of subjects enrolled	Greece: 30
Country: Number of subjects enrolled	Hong Kong: 21
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	India: 29
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 64
Country: Number of subjects enrolled	Italy: 117
Country: Number of subjects enrolled	Latvia: 21
Country: Number of subjects enrolled	Lithuania: 23
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 8
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Poland: 15

Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 178
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	Austria: 38
Country: Number of subjects enrolled	Bulgaria: 14
Worldwide total number of subjects	1021
EEA total number of subjects	683

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)	763
From 65 to 84 years	258
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1094 participants were screened and of these, 73 participants failed screening and the remaining 1021 were enrolled in the study. This study has been completed. However, the efficacy and safety results up to the clinical database cutoff date of 07 December 2014 are provided.

Period 1

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

Arms

Arm title	Bevacizumab + Paclitaxel + Carboplatin
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Arm description:

Participants received bevacizumab 15 milligrams/kilogram (mg/kg) intravenously (IV) on Day 1 every 3 weeks from Cycle 1 (1 cycle = 3 weeks) to Cycle 36 (initially concurrent with chemotherapy, then continued as a single agent following the completion of chemotherapy), or until protocol-defined disease progression or until unacceptable toxicity (whichever occurred first). The 15 mg/kg dose every 3 weeks was the recommended dose; however a dose of IV bevacizumab 7.5 mg/kg every 3 weeks was permissible, but was to be selected prior to the first dosing of bevacizumab. Participants received paclitaxel 175 milligram per square meter (mg/m²) IV on Day 1 every 3 weeks or 80 mg/m² IV every week and carboplatin (area under the plasma concentration-time curve [AUC] 5-6) IV on Day 1 every 3 weeks for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol-defined disease progression, or unacceptable toxicity (whichever occurred first).

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

Dosage and administration details:

Participants received paclitaxel 175 mg/m² IV on Day 1 every 3 weeks or 80 mg/m² every week for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol-defined disease progression, or unacceptable toxicity (whichever occurred first).

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

Dosage and administration details:

Participants received carboplatin (AUC 5-6) IV on Day 1 every 3 weeks for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol-defined disease progression, or unacceptable toxicity (whichever occurred first).

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

Dosage and administration details:

Participants received bevacizumab 15mg/kg IV on Day 1 every 3 weeks from Cycle 1 to Cycle 36

(initially concurrent with chemotherapy, then continued as a single agent following the completion of chemotherapy), or until protocol-defined disease progression or until unacceptable toxicity (whichever occurred first). The 15 mg/kg dose every 3 weeks was the recommended dose; however a dose of IV bevacizumab 7.5 mg/kg every 3 weeks was permissible, but was to be selected prior to the first dosing of bevacizumab.

Number of subjects in period 1	Bevacizumab + Paclitaxel + Carboplatin
Started	1021
Completed	0
Not completed	1021
Participant non compliance	5
Consent withdrawn by subject	87
Investigator's decision	4
Termination of study per protocol	667
Adverse Event	6
Treatment failure	2
Protocol violation	3
Death	226
Unspecified	19
Study termination by sponsor	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Study (overall period)
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Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 every 3 weeks from Cycle 1 (1 cycle = 3 weeks) to Cycle 36 (initially concurrent with chemotherapy, then continued as a single agent following the completion of chemotherapy), or until protocol-defined disease progression or until unacceptable toxicity (whichever occurred first). The 15 mg/kg dose every 3 weeks was the recommended dose; however a dose of IV bevacizumab 7.5 mg/kg every 3 weeks was permissible, but was to be selected prior to the first dosing of bevacizumab. Participants received paclitaxel 175 mg/m² IV on Day 1 every 3 weeks or 80 mg/m² IV every week and carboplatin (AUC 5-6) IV on Day 1 every 3 weeks for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol-defined disease progression, or unacceptable toxicity (whichever occurred first).

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	1021	1021	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	56.3 ± 10.98	-	
Gender categorical Units: Subjects			
Female	1021	1021	
Male	0	0	

End points

End points reporting groups

Reporting group title	Bevacizumab + Paclitaxel + Carboplatin
Reporting group description:	
Participants received bevacizumab 15 milligrams/kilogram (mg/kg) intravenously (IV) on Day 1 every 3 weeks from Cycle 1 (1 cycle = 3 weeks) to Cycle 36 (initially concurrent with chemotherapy, then continued as a single agent following the completion of chemotherapy), or until protocol-defined disease progression or until unacceptable toxicity (whichever occurred first). The 15 mg/kg dose every 3 weeks was the recommended dose; however a dose of IV bevacizumab 7.5 mg/kg every 3 weeks was permissible, but was to be selected prior to the first dosing of bevacizumab. Participants received paclitaxel 175 milligram per square meter (mg/m ²) IV on Day 1 every 3 weeks or 80 mg/m ² IV every week and carboplatin (area under the plasma concentration-time curve [AUC] 5-6) IV on Day 1 every 3 weeks for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol-defined disease progression, or unacceptable toxicity (whichever occurred first).	

Primary: Percentage of Participants With at Least One Adverse Event (AE)

End point title	Percentage of Participants With at Least One Adverse Event (AE) ^[1]
End point description:	
An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Analysis was performed on safety population, which included all participants who received at least one dose of study medication.	
End point type	Primary
End point timeframe:	
Day 1 up to 30 days after last dose of study treatment (until data cutoff 07 December 2014, up to 4 years)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this endpoint.

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	1021			
Units: percentage of participants				
number (not applicable)	97.8			

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 time between the date of first administration of any study treatment and the date of first documented protocol defined disease progression (that is [i.e.], radiologically by Response Evaluation Criteria In Solid Tumors [RECIST], clinical, or symptomatic) or death, whichever occurred first. Participants who had neither progressed nor died at the time of data cut-off (07 December 2014),	

or participants who were withdrawn from study, or lost to follow-up without documented progression, were censored. Kaplan-Meier estimation was used for median time to PFS. Analysis was performed on intent to treat population (ITT), which included all participants who received at least one dose of study medication.

End point type	Secondary
End point timeframe:	
Day 1, at end of Cycles 3 and 6, then every 6 cycles while receiving bevacizumab, and then at bevacizumab cessation, every 26 weeks after cessation of bevacizumab until disease progression or death until data cutoff 07 December 2014, up to 4 years	

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	1021			
Units: months				
median (confidence interval 95%)	25.5 (23.7 to 27.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0

End point title	Percentage of Participants Achieving Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0
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End point description:

Best overall response (BOR) per RECIST version 1.0 was categorized as: CR, PR, progressive disease (PD), stable disease (SD). CR: disappearance of all target lesions and non-target lesions. PR: greater than or equal to ($\geq$) 30 percent (%) decrease in sum of the longest diameters (LD) of the target lesions taking as a reference the baseline sum LD according to RECIST associated to non-progressive disease response for non-target lesions. PD: Natural progression or deterioration of the malignancy under study (including new sites of metastasis). SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. Participants with a BOR of CR and PR were defined as responders, while participants with a BOR of SD, PD, or unable to assess were defined as non-responders. Analysis was performed on ITT population. Number of participants analyzed = participants who were evaluable for this outcome.

End point type	Secondary
End point timeframe:	
Day 1, at end of Cycles 3 and 6, then every 6 cycles while receiving bevacizumab, and then at bevacizumab cessation, every 26 weeks (Q26W) after cessation of bevacizumab until disease progression or death until data cutoff 07 December 2014, up to 4 years	

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	421			
Units: percentage of participants				
number (confidence interval 95%)	72.7 (68.2 to 76.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an Overall Response by 50% Carcinoma Antigen 125 (CA-125) Response Criteria

End point title	Percentage of Participants Achieving an Overall Response by 50% Carcinoma Antigen 125 (CA-125) Response Criteria
End point description:	
CA-125 responders: Participants with the value of CA-125 reduced by at least 50% and confirmed with a consecutive CA-125 assessment performed at an interval of at least 28 days. Overall response according to CA-125 was only evaluated for participants with a pre-treatment CA-125 within 3 days prior to start of any study treatment of at least twice the upper limit of normal (ULN). Analysis was performed on ITT population. Number of participants analyzed = participants who were evaluable for this outcome.	
End point type	Secondary
End point timeframe:	
3 days prior to Day 1 of every cycle, then every 6 weeks (Q6W) during the first year, every 3 months (Q3M) in the second and third year, every 6 months (Q6M) in the fourth year of the study (until data cutoff 07 December 2014, up to 4 years)	

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	340			
Units: percentage of participants				
number (confidence interval 95%)	91.8 (88.3 to 94.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an Overall Response by RECIST Version 1.0 and/or 50% CA-125 Response Criteria

End point title	Percentage of Participants Achieving an Overall Response by RECIST Version 1.0 and/or 50% CA-125 Response Criteria
End point description:	
Overall response was only evaluated for participants who were evaluable according to RECIST version 1.0 with a measurable disease at baseline and/or according to CA-125 with a pre-treatment CA-125	

within 3 days prior to start of any study treatment of at least twice the ULN. RECIST responders: Participants achieving an overall response of CR (disappearance of all target lesions and non-target lesions) or PR ($\geq 30\%$ decrease in sum of the LD of the target lesions taking as a reference the baseline sum LD according to RECIST associated to non-progressive disease response for non target lesions). CA-125 responders: Participants with the value of CA-125 reduced by at least 50% and confirmed with a consecutive CA-125 assessment performed at an interval of at least 28 days. Analysis was performed on ITT population. Number of participants analyzed = participants who were evaluable for this outcome.

End point type	Secondary
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End point timeframe:

RECIST: Day 1, at end of Cycles 3 and 6, then every 6 cycles, at bevacizumab cessation, Q26W after cessation; CA-125: 3 days before Day 1 of every cycle, then Q6W(1st year), Q3M(2nd-3rd year), Q6M(4th year); until data cutoff 07Dec2014, up to 4 years

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	578			
Units: percentage of participants				
number (confidence interval 95%)	82.4 (79 to 85.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)
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End point description:

DOR was defined as the time from the first documented response (CR or PR per RECIST version 1.0), to the first documented protocol defined disease progression (i.e., radiologically by RECIST, clinical, or symptomatic) or death, whichever occurred first. Participants who had neither progressed nor died at the time of data cut-off (07 December 2014), or participants who were withdrawn from study, or lost to follow-up without documented progression, were censored. RECIST responders: Participants achieving an overall response of CR (disappearance of all target lesions and non-target lesions) or PR ($\geq 30\%$ decrease in sum of the LD of the target lesions taking as a reference the baseline sum LD according to RECIST associated to non-progressive disease response for non target lesions). Disease progression: Natural progression or deterioration of the malignancy under study (including new sites of metastasis). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Day 1, at end of Cycles 3 and 6, then every 6 cycles while receiving bevacizumab, and then at bevacizumab cessation, every 26 weeks after cessation of bevacizumab until disease progression or death until data cutoff 07 December 2014, up to 4 years

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	1021			
Units: months				
median (confidence interval 95%)	18.2 (16.6 to 19.6)			

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 time from the date of the first administration of any study treatment to the date of death, regardless of the cause of death. Participants without the event of death were censored at the last date in the study, defined as the latest date of the following: the date of first administration of study treatment, date of last study treatment, date of last visit, or date last known to be alive. Kaplan-Meier estimation was used for OS. Analysis was performed on ITT population. "99999" signifies the median and 95% confidence interval were not calculable because less than 50% of participants had the event.	
End point type	Secondary
End point timeframe:	
First administration of any study treatment until death or data cutoff 07 December 2014, up to 4 years	

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	1021			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Biological Progression-free Interval

End point title	Biological Progression-free Interval
End point description:	
Biological progression-free interval is defined as the interval from the date of the first administration of any study treatment to the date of the first documented serial elevation of the ovarian cancer mucin CA-125. More precisely, this is defined as the first documented increase in CA-125 levels as follows: 1) CA-125 ≥ 2 times (x) the ULN on 2 occasions at least 1 week apart (for participants with CA-125 within normal range pre-treatment) or 2) CA-125 $\geq 2 \times$ ULN on 2 occasions at least 1 week apart (for participants with elevated CA-125 pre-treatment and initial normalization of CA-125 on-treatment) or 3) CA-125 $\geq 2 \times$ nadir value, which is the lowest observed CA-125 value per participant on 2 occasions at	

least 1 week apart (for participants with elevated CA-125 pre-treatment which never normalized). Studies linking CA-125 levels with bevacizumab exposure for PFS did not produce any reliable information. Therefore, biological PFS data were not analyzed.

End point type	Secondary
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End point timeframe:

3 days prior to Day 1 of every cycle, then every 6 weeks during the first year, every 3 months in the second and third year, every 6 months in the fourth year of the study (until data cutoff 07 December 2014, up to 4 years)

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[2]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[2] - The data of biological progression-free interval were not analyzed for this study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 30 days after last dose of study treatment (until data cutoff 07 December 2014, up to 4 years)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Bevacizumab + Paclitaxel + Carboplatin
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Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 every 3 weeks from Cycle 1 (1 cycle = 3 weeks) to Cycle 36 (initially concurrent with chemotherapy, then continued as a single agent following the completion of chemotherapy), or until protocol defined disease progression or until unacceptable toxicity (whichever occurred first). The 15 mg/kg dose every 3 weeks was the recommended dose; however a dose of IV bevacizumab 7.5 mg/kg every 3 weeks was permissible, but was to be selected prior to the first dosing of bevacizumab. Participants received paclitaxel 175 mg/m² IV on Day 1 every 3 weeks or 80 mg/m² IV every week and carboplatin (AUC 5-6) IV on Day 1 every 3 weeks for a minimum of 4 and maximum of 8 cycles (including up to 4 pre-surgical cycles), or until protocol defined disease progression, or unacceptable toxicity (whichever occurred first).

Serious adverse events	Bevacizumab + Paclitaxel + Carboplatin		
Total subjects affected by serious adverse events			
subjects affected / exposed	285 / 1021 (27.91%)		
number of deaths (all causes)	235		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer recurrent			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 1021 (1.57%)		
occurrences causally related to treatment / all	14 / 16		
deaths causally related to treatment / all	0 / 0		
Embolism venous			
subjects affected / exposed	9 / 1021 (0.88%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	1 / 1		
Lymphocele			
subjects affected / exposed	8 / 1021 (0.78%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism arterial			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arterial thrombosis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant hypertension			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Intestinal operation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 1021 (0.59%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		

General physical health deterioration				
subjects affected / exposed	4 / 1021 (0.39%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Impaired healing				
subjects affected / exposed	2 / 1021 (0.20%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	2 / 1021 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Fatigue				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Drug hypersensitivity			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	8 / 1021 (0.78%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bruxism			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase abnormal			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood alkaline phosphatase abnormal subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical condition abnormal subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Lower limb fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seroma			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion reaction			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Angina pectoris			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			

subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular disorder			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Lacunar infarction			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukoencephalopathy			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensorimotor neuropathy			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	25 / 1021 (2.45%)		
occurrences causally related to treatment / all	6 / 28		
deaths causally related to treatment / all	0 / 1		
Neutropenia			
subjects affected / exposed	21 / 1021 (2.06%)		
occurrences causally related to treatment / all	7 / 23		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	16 / 1021 (1.57%)		
occurrences causally related to treatment / all	3 / 20		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	13 / 1021 (1.27%)		
occurrences causally related to treatment / all	3 / 14		
deaths causally related to treatment / all	0 / 0		
Leukopenia			

subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombotic microangiopathy			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pancytopenia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 1021 (1.27%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	11 / 1021 (1.08%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	9 / 1021 (0.88%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 1		
Subileus			
subjects affected / exposed	9 / 1021 (0.88%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			

subjects affected / exposed	8 / 1021 (0.78%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	8 / 1021 (0.78%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	6 / 1021 (0.59%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	5 / 1021 (0.49%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	4 / 1021 (0.39%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			

subjects affected / exposed	2 / 1021 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal incarcerated hernia				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis haemorrhagic				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric stenosis				

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal toxicity			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jejunal perforation			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mechanical ileus			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Erythema			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraneoplastic dermatomyositis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Renal failure			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Calculus ureteric			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal infarct			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteric obstruction			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Arthropathy				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rheumatic disorder				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	5 / 1021 (0.49%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	5 / 1021 (0.49%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Infected lymphocele				
subjects affected / exposed	4 / 1021 (0.39%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	3 / 1021 (0.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal wall abscess			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection			

subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal infection			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal sepsis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute hepatitis C			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis infective			

subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colonic abscess				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 1021 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gingivitis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Groin abscess			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected cyst			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotid abscess			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal abscess			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Staphylococcal infection			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulval cellulitis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis infectious			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 1021 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			

subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nicotinic acid deficiency			
subjects affected / exposed	1 / 1021 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab + Paclitaxel + Carboplatin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	980 / 1021 (95.98%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	552 / 1021 (54.06%)		
occurrences (all)	1429		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	372 / 1021 (36.43%)		
occurrences (all)	637		
Asthenia			
subjects affected / exposed	135 / 1021 (13.22%)		
occurrences (all)	243		
Mucosal inflammation			

subjects affected / exposed	110 / 1021 (10.77%)		
occurrences (all)	140		
Pyrexia			
subjects affected / exposed	86 / 1021 (8.42%)		
occurrences (all)	109		
Oedema peripheral			
subjects affected / exposed	63 / 1021 (6.17%)		
occurrences (all)	72		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	301 / 1021 (29.48%)		
occurrences (all)	461		
Cough			
subjects affected / exposed	94 / 1021 (9.21%)		
occurrences (all)	125		
Dyspnoea			
subjects affected / exposed	66 / 1021 (6.46%)		
occurrences (all)	83		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	66 / 1021 (6.46%)		
occurrences (all)	79		
Investigations			
Weight increased			
subjects affected / exposed	77 / 1021 (7.54%)		
occurrences (all)	81		
Platelet count decreased			
subjects affected / exposed	93 / 1021 (9.11%)		
occurrences (all)	164		
Nervous system disorders			
Headache			
subjects affected / exposed	241 / 1021 (23.60%)		
occurrences (all)	449		
Neuropathy peripheral			

subjects affected / exposed	201 / 1021 (19.69%)		
occurrences (all)	268		
Peripheral sensory neuropathy			
subjects affected / exposed	161 / 1021 (15.77%)		
occurrences (all)	205		
Paraesthesia			
subjects affected / exposed	134 / 1021 (13.12%)		
occurrences (all)	195		
Dizziness			
subjects affected / exposed	75 / 1021 (7.35%)		
occurrences (all)	88		
Dysgeusia			
subjects affected / exposed	68 / 1021 (6.66%)		
occurrences (all)	94		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	485 / 1021 (47.50%)		
occurrences (all)	1046		
Anaemia			
subjects affected / exposed	333 / 1021 (32.62%)		
occurrences (all)	471		
Thrombocytopenia			
subjects affected / exposed	279 / 1021 (27.33%)		
occurrences (all)	560		
Leukopenia			
subjects affected / exposed	109 / 1021 (10.68%)		
occurrences (all)	245		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	393 / 1021 (38.49%)		
occurrences (all)	863		
Diarrhoea			
subjects affected / exposed	258 / 1021 (25.27%)		
occurrences (all)	480		

Constipation subjects affected / exposed occurrences (all)	255 / 1021 (24.98%) 441		
Vomiting subjects affected / exposed occurrences (all)	230 / 1021 (22.53%) 370		
Abdominal pain subjects affected / exposed occurrences (all)	221 / 1021 (21.65%) 341		
Stomatitis subjects affected / exposed occurrences (all)	110 / 1021 (10.77%) 165		
Abdominal pain upper subjects affected / exposed occurrences (all)	104 / 1021 (10.19%) 143		
Gingival bleeding subjects affected / exposed occurrences (all)	75 / 1021 (7.35%) 107		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	442 / 1021 (43.29%) 450		
Rash subjects affected / exposed occurrences (all)	76 / 1021 (7.44%) 101		
Pruritus subjects affected / exposed occurrences (all)	71 / 1021 (6.95%) 101		
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	317 / 1021 (31.05%) 681		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	261 / 1021 (25.56%)		
occurrences (all)	439		
Myalgia			
subjects affected / exposed	185 / 1021 (18.12%)		
occurrences (all)	304		
Pain in extremity			
subjects affected / exposed	138 / 1021 (13.52%)		
occurrences (all)	198		
Back pain			
subjects affected / exposed	133 / 1021 (13.03%)		
occurrences (all)	163		
Musculoskeletal pain			
subjects affected / exposed	132 / 1021 (12.93%)		
occurrences (all)	189		
Bone pain			
subjects affected / exposed	52 / 1021 (5.09%)		
occurrences (all)	67		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	122 / 1021 (11.95%)		
occurrences (all)	181		
Nasopharyngitis			
subjects affected / exposed	83 / 1021 (8.13%)		
occurrences (all)	114		
Upper respiratory tract infection			
subjects affected / exposed	60 / 1021 (5.88%)		
occurrences (all)	92		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	94 / 1021 (9.21%)		
occurrences (all)	123		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2011	- The recommended dose of bevacizumab remained as 15 mg/kg; however; the investigator was permitted to use a bevacizumab dose of 7.5 mg/kg instead. - Guidance on the assessment of glomerular filtration rate and thus carboplatin dose was provided, after a change in the standards of the laboratory testing of creatinine; which could have impacted the dose of carboplatin given. - Clarification of what concomitant medication is required to be documented in the electronic case report forms (eCRF). - Clarification of the maximum number of bevacizumab monotherapy cycles to be received and that there was no stipulated minimum. - Clarification that the participant must remain on the commenced paclitaxel regimen (every 3 weeks or weekly) for the duration of paclitaxel therapy.
21 February 2012	- Regarding thromboembolic events: The exclusion criteria were updated to specify that participants who had recent (within 6 months) Grade >1 arterial or Grade >3 venous thromboembolic events were excluded. This aligned the MO22923 study with other bevacizumab study protocols which excluded participants with recent thromboses. The guidance of when to stop bevacizumab therapy following thromboembolic events was further clarified so that pulmonary emboli were specified as venous events and that dose adjustment for asymptomatic venous thromboembolic events found on routine scans were done on a case-by-case basis according to the judgment of the investigator. - Regarding hematology lab value requirements for paclitaxel administration: During amendment Version 2.0 the absolute neutrophil count (ANC) levels to withhold paclitaxel dose were incorrectly changed from $1.0 \times 10^9/L$ to $1.5 \times 10^9/L$. Feedback from investigators revealed that this was not in accordance with common practice and led to many doses being unnecessarily missed or numerous protocol violations. The ANC level for withholding paclitaxel was re-set to $1.0 \times 10^9/L$. The entry level ANC for the study remained at $1.5 \times 10^9/L$. In addition, the minimum platelets level on Days 8 and 15, used to determine paclitaxel administration was changed from $100 \times 10^9/L$ to $80 \times 10^9/L$. - The exploratory biomarker analyses were supplemented with additional samples to be taken during bevacizumab monotherapy for those participants who consented to be in the biomarker study.
25 February 2014	Greater clarity was provided regarding the End of Study - The protocol was aligned with the updated biomarker plan which no longer included immunohistochemistry analyses (e.g., vascular endothelial growth factor [VEGF], VEGF receptor 1/2 [VEGFR1/2], neuropilin-1, cluster of differentiation 31 [CD31]) from tissue samples. The updated biomarker plan focused on ribonucleic acid (RNA) extraction. The planned analysis of tissue-derived deoxyribonucleic acid (DNA) was removed. - The post-study provision of care with bevacizumab was clarified. - Definition of the per protocol (PP) population was clarified. - Text regarding the reporting and follow up of AEs was updated in line with the latest Roche protocol template wording.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported