Clinical trial results:
An open-label phase IIIb study of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy

Summary

EudraCT number	2011-005836-25
Trial protocol	BE DE CZ ES GB IT AT NL IE FR PT FI SE GR HU PL DK
Global end of trial date	30 April 2019

Results information

Result version number	v3 (current)
This version publication date	22 January 2020
First version publication date	02 July 2016
Version creation reason	• Correction of full data set CSR updated after study completion

Trial information

Trial identification

Sponsor protocol code	BAY73-4506 / 15967

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01538680
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	30 April 2019
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were:
- to provide regorafenib to subjects diagnosed with metastatic colorectal cancer who had failed after all approved standard therapies,
- to assess the safety of regorafenib, and
- to estimate progression-free survival (PFS).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 87
Country: Number of subjects enrolled	Austria: 46
Country: Number of subjects enrolled	Belgium: 172
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 329
Country: Number of subjects enrolled	Germany: 327
Country: Number of subjects enrolled	Greece: 28
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Italy: 686
Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 7

Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Spain: 308
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 39
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Israel: 113
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	United States: 364
Worldwide total number of subjects	2872
EEA total number of subjects	2088

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)	1720
From 65 to 84 years	1152
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at centers in Europe, North America (including Mexico), Israel, and Australia. From 02 April 2012 (first subject first visit) to 30 April 2019 (date of last visit).

Pre-assignment

Screening details:

Overall, 3309 subjects were screened and enrolled. Of these, a total of 2872 subjects were assigned to receive treatment (trt). A total of 2864 subjects started treatment, and all terminated the treatment.

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	Regorafenib (BAY73-4506)

Arm description:

Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator’s opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator’s discretion.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received regorafenib 160 mg (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (i.e. 3 weeks on, 1 week off).

Number of subjects in period 1	Regorafenib (BAY73-4506)
Started	2872
Started treatment	2864
Start safety follow-up	1597
Safety follow-up completed	374
Completed	0
Not completed	2872
Adverse event associated with clinical disease	405
Physician decision	11

Adverse event not associated with clinical dis	327
Protocol driven decision point	5
Not specified	4
Study terminated by sponsor	1
Progressive disease - radiological progression	1640
Withdrawal by subject	212
Therapeutic procedure required	3
Progressive disease - clinical progression	205
Protocol violation	5
Death	1
Non-compliance with study drug	4
Switching to other therapy	1
Never treated	8
Lost to follow-up	40

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib (BAY73-4506)

Reporting group description:

Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator's opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator's discretion.

Reporting group values	Regorafenib (BAY73-4506)	Total	
Number of subjects	2872	2872	
Age categorical Units: Subjects			
Total Units: years			
arithmetic mean	61.1		
standard deviation	± 10.5	-	
Gender, Male/Female Units: subjects			
Female	1180	1180	
Male	1692	1692	
Eastern Cooperative Oncology Group (ECOG) performance status (PS)			
ECOG PS score was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death.			
Units: Subjects			
0 = Fully Active	1357	1357	
1= Restricted Activity	1509	1509	
Missing	6	6	
Histology			
Subjects with relating to disease factors includes Adenocarcinoma, Adenocarcinoma In Situ, Mucinous Carcinoma, Missing were reported.			
Units: Subjects			
Adenocarcinoma	2852	2852	
Adenocarcinoma In Situ	15	15	
Mucinous Carcinoma	3	3	
Missing	2	2	
Primary Site of Disease			
Subjects with primary site of disease (Colon, Rectum, Colon and Rectum) were reported.			
Units: Subjects			
Colon Cancer	1846	1846	

Rectal Cancer	808	808	
Colon and Rectal Cancer	217	217	
Missing	1	1	
Kirsten rat sarcoma viral oncogene homolog, protein (KRAS) Mutation			
KRAS Mutation was defined as historical data from the primary tumor, analyzed in local laboratories.			
Units: Subjects			
No	1284	1284	
Yes	1465	1465	
Unknown	122	122	
Missing	1	1	
Time Since Initial Diagnosis of Colorectal Cancer to Treatment Assignment			
Treatment assignment was the date of first treatment.			
Units: Subjects			
Less than (<) 18 months	315	315	
Greater than equal (≥)18 months	2549	2549	
Missing	8	8	
Time Since First Diagnosis of Metastatic Disease to Treatment Assignment			
Units: weeks			
arithmetic mean	158.39		
standard deviation	± 99.32	-	

End points

End points reporting groups

Reporting group title	Regorafenib (BAY73-4506)

Reporting group description:

Subjects received regorafenib 160 milligram (mg) (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off). Subjects continued in the study until at least one of the following occurred: PD by radiological assessments or clinical progression (only the date of progression and the presence/absence of new/progressive brain and liver metastases were recorded); death; unacceptable toxicity; subject withdrew consent; treating physician determined discontinuation of treatment was in the subject's best interest; substantial non-compliance with the protocol or until other withdrawal criterion was met. If, in the investigator’s opinion, treatment with regorafenib was providing clinical benefit to a subject experiencing disease progression, the subject may have continued treatment at the investigator’s discretion.

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation, and Drug Related TEAEs, and Subjects Who Died

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), TEAEs Leading to Discontinuation, and Drug Related TEAEs, and Subjects Who Died[1]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another med important serious event as judged by the invest. Treatment-emergent was defined as any event arising or worsening after the start of study drug admin until 30 days after the last study medication. Safety analysis set (SAF) included all subjects who received at least one dose of study drug. Number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment up to 30 days after the last dose of study drug, assessed up to 33 months

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: subjects				
number (not applicable)				
TEAEs	2847			
TESAEs	1253			
TEAEs leading to discontinuation of drug	724			
Drug related TEAEs	2613			
Subjects who died (Grade 5 TEAEs)	406			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-emergent High Laboratory Abnormalities (TELA)

End point title	Percentage of Subjects With Treatment-emergent High Laboratory Abnormalities (TELA)[2]

End point description:

A TELA was any abnormal event arising after the start of study drug administration, which focused on coagulation, general chemistry, hematology, hormone panels and thyroid function test. The denominator (D) represents the number of subjects at baseline with a normal or lower than normal laboratory assessment (LA) who also had at least one valid laboratory value after start of treatment. Subjects with missing or high abnormal values at baseline are not included in the D. The numerator represents the number of subjects with at least one high LA after the start of treatment who had a normal or lower than normal LA at baseline. If there are repeated observations prior to first study drug intake, baseline is defined as the last non-missing pre-treatment measurement, where baseline cannot be set on the same date as the first study drug intake. SAF, number of subjects analyzed signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

From the start of study treatment up to 14 days after the last dose of study drug

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: percentage of subjects				
number (not applicable)				
Activated Partial Thromboplastin Time (n=1745)	23.7			
Prothrombin Intl. Normalized Ratio (n=1719)	20.9			
Prothrombin Time (n=684)	29.2			
Alanine Aminotransferase (n=2049)	44.0			
Alkaline Phosphatase (n=993)	48.6			
Aspartate Aminotransferase (n=1630)	61.4			
Bilirubin (n=2290)	58.2			
Calcium (n=2266)	3.5			
Chloride (n=2225)	11.2			
Creatinine (n=2240)	12.9			
Direct Bilirubin (n=1368)	61.9			
Phosphate (n=2111)	3.9			
Potassium (n=2312)	13.4			
Sodium (n=2392)	5			

Triacylglycerol Lipase (n=2138)	37.6			
Basophils (n=1878)	5.6			
Basophils/Leukocytes (n=695)	8.3			
Eosinophils (n=1773)	13.8			
Eosinophils/Leukocytes (n=642)	20.7			
Erythrocytes (n=2374)	10.4			
Hematocrit (n=2394)	7.5			
Hemoglobin (n=2417)	5.3			
Leukocytes (n=2018)	36.6			
Lymphocytes (n=1941)	2.6			
Lymphocytes/Leukocytes (n=715)	2.5			
Monocytes (n=1593)	31.5			
Monocytes/Leukocytes (n=558)	35.1			
Neutrophils (n=1607)	38.2			
Neutrophils/Leukocytes (n=507)	49.7			
Platelets (n=2215)	15.5			
Thyrotropin (n=1805)	36.4			
Thyroxine, Free (n=1611)	9.9			
Triiodothyronine, Free (n=1382)	4.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-emergent Low Laboratory Abnormalities (TELA)

End point title	Percentage of Subjects With Treatment-emergent Low Laboratory Abnormalities (TELA)[3]

End point description:

A TELA was any abnormal event arising after the start of study drug administration, which focused on coagulation, general chemistry, hematology, hormone panels and thyroid function test. The D represents the number of subjects at baseline with a normal or higher than normal LA who also had at least one valid laboratory value after start of treatment. Subjects with missing or low abnormal values at baseline are not included in the D. The numerator represents the number of subjects with at least one low LA after the start of treatment who had a normal or higher than normal LA at baseline. If there are repeated observations prior to first study drug intake, baseline is defined as the last non-missing pre-treatment measurement, where baseline cannot be set on the same date as the first study drug intake. SAF, number of subjects analyzed signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

From the start of study treatment up to 14 days after the last dose of study drug

Notes:

[3] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: percentage of subjects				
number (not applicable)				
Activated Partial Thromboplastin Time (n=1905)	7.9			
Prothrombin Intl. Normalized Ratio (n=1884)	1.8			
Prothrombin Time (n=771)	4.2			
Alanine Aminotransferase (n=2402)	4.1			
Alkaline Phosphatase (n=2407)	0.9			
Aspartate Aminotransferase (n=2449)	1			
Bilirubin (n=2437)	1.2			
Calcium (n=2226)	44.1			
Chloride (n=2070)	30.0			
Creatinine (n=2149)	23.8			
Direct Bilirubin (n=1736)	0.2			
Phosphate (n=2009)	69.1			
Potassium (n=2312)	27.8			
Sodium (n=2220)	36.1			
Triacylglycerol Lipase (n=2150)	7.1			
Basophils (n=1879)	2.5			
Basophils/Leukocytes (n=701)	2			
Eosinophils (n=1849)	10.4			
Eosinophils/Leukocytes (n=636)	18.9			
Erythrocytes (n=1351)	39.6			
Hematocrit (n=1360)	48.1			
Hemoglobin (n=1262)	45.2			
Leukocytes (n=2343)	13.2			
Lymphocytes (n=1388)	39.3			
Lymphocytes/Leukocytes (n=369)	56.1			
Monocytes (n=1920)	3.9			
Monocytes/Leukocytes (n=714)	7.6			
Neutrophils (n=1968)	5.9			
Neutrophils/Leukocytes (n=714)	4.1			
Platelets (n=2169)	30.1			
Thyrotropin (n=1926)	4.8			
Thyroxine, Free (n=1644)	4.9			
Triiodothyronine, Free (n=1285)	18.8			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Heart Rate at Specified Time Points

End point title	Change From Baseline in Heart Rate at Specified Time Points[4]

End point description:

SAF, Here “N” (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n"

signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

End point type	Primary

End point timeframe:

Baseline, Day 1 (Cycle 1 to 33), and end of treatment

Notes:

[4] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2812			
Units: beats per minute				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n = 1067)	-0.4 (± 10.8)			
Cycle 2 Day 1 (n = 1915)	2.4 (± 13)			
Cycle 3 Day 1 (n = 1376)	1.8 (± 12.6)			
Cycle 4 Day 1 (n = 927)	1.4 (± 13.2)			
Cycle 5 Day 1 (n = 651)	1.4 (± 12.8)			
Cycle 6 Day 1 (n = 503)	1.1 (± 12.8)			
Cycle 7 Day 1 (n = 364)	0.9 (± 13.4)			
Cycle 8 Day 1 (n = 287)	0.4 (± 14)			
Cycle 9 Day 1 (n = 234)	1 (± 13)			
Cycle 10 Day 1 (n = 189)	1.2 (± 12.6)			
Cycle 11 Day 1 (n = 157)	0.2 (± 12.9)			
Cycle 12 Day 1 (n = 136)	1.1 (± 12.1)			
Cycle 13 Day 1 (n = 110)	1.4 (± 13.8)			
Cycle 14 Day 1 (n = 88)	1.3 (± 11.7)			
Cycle 15 Day 1 (n = 73)	1.3 (± 13.6)			
Cycle 16 Day 1 (n = 60)	0.2 (± 13.8)			
Cycle 17 Day 1 (n = 52)	1.4 (± 13.6)			
Cycle 18 Day 1 (n = 43)	0.4 (± 12.7)			
Cycle 20 Day 1 (n = 28)	1.3 (± 13.0)			
Cycle 21 Day 1 (n = 24)	3.7 (± 14.3)			
Cycle 19 Day 1 (n=37)	1.3 (± 13.0)			
Cycle 22 Day 1 (n=20)	2.8 (± 10)			
Cycle 23 Day 1 (n=16)	-1.3 (± 13.1)			
Cycle 24 Day 1 (n=14)	-1.1 (± 10.6)			
Cycle 25 Day 1 (n=14)	1.2 (± 11.2)			
Cylce 26 Day 1 (n=13)	0.9 (± 12.8)			
Cylce 27 Day 1 (n=11)	-2.5 (± 9.2)			
Cylce 28 Day 1 (n=11)	0.9 (± 11.9)			
Cylce 29 Day 1 (n=10)	-4.1 (± 9)			
Cylce 30 Day 1 (n=10)	-1.1 (± 12.7)			
Cylce 31 Day 1 (n=7)	-2.7 (± 8.7)			
Cylce 32 Day 1 (n=7)	-0.4 (± 5.4)			
Cylce 33 Day 1 (n=7)	-3.7 (± 6.6)			
End of treatment (n=1477)	4.4 (± 14.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Diastolic Blood Pressure at Specified Time Points

End point title	Change From Baseline in Diastolic Blood Pressure at Specified Time Points[5]

End point description:

SAF, Here "N" (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

End point type	Primary

End point timeframe:

Baseline, Cycle 1 Days 1, 8, 15, 22; Cycle 2 Days 1, 8, 15; Cycle 3 to 33 (Day 1), and End of treatment

Notes:

[5] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=1096)	-0.3 (± 7.8)			
Cycle 1 Day 8 (n=1896)	4.1 (± 11)			
Cycle 1 Day 15 (n=2146)	3.6 (± 11.5)			
Cycle 1 Day 22 (n=1578)	2.4 (± 10.5)			
Cycle 2 Day 1 (n=1976)	0 (± 10.2)			
Cycle 2 Day 8 (n=1343)	3.1 (± 11.2)			
Cycle 2 Day 15 (n=1724)	3.3 (± 10.5)			
Cycle 3 Day 1 (n=1412)	-1.2 (± 10.2)			
Cycle 4 Day 1 (n=959)	-1 (± 10.2)			
Cycle 5 Day 1 (n=674)	-1.5 (± 9.6)			
Cycle 6 Day 1 (n=527)	-0.9 (± 10.4)			
Cycle 7 Day 1 (n=374)	-1 (± 10.4)			
Cycle 8 Day 1 (n=297)	-1.7 (± 11.2)			
Cycle 9 Day 1 (n=248)	-1.3 (± 10.3)			
Cycle 10 Day 1 (n=197)	-0.8 (± 10.3)			
Cycle 11 Day 1 (n=163)	-1 (± 10.3)			
Cycle 12 Day 1 (n=143)	-1.2 (± 10.6)			
Cycle 13 Day 1 (n=113)	-1.9 (± 10.6)			
Cycle 14 Day 1 (n=92)	-2.1 (± 9.9)			
Cycle 15 Day 1 (n=78)	-1.6 (± 10.5)			
Cycle 16 Day 1 (n=63)	-5.5 (± 10.7)			
Cycle 17 Day 1 (n=54)	-2.7 (± 11)			

Cycle 18 Day 1 (n=44)	-2.4 (± 11.7)			
Cycle 19 Day 1 (n=37)	-3.4 (± 12.1)			
Cycle 20 Day 1 (n=29)	-1.4 (± 10.5)			
Cycle 21 Day 1 (n=24)	-0.7 (± 12.4)			
Cycle 22 Day 1 (n=20)	-5.9 (± 12.7)			
Cycle 23 Day 1 (n=16)	-4.6 (± 10.2)			
Cycle 24 Day 1 (n=14)	-2.9 (± 10.8)			
Cycle 25 Day 1 (n=14)	-5.0 (± 11.9)			
Cycle 26 Day 1 (n=13)	-5.2 (± 11.0)			
Cycle 27 Day 1 (n=11)	-3.8 (± 11.3)			
Cycle 28 Day 1 (n=11)	-6 (± 11.2)			
Cycle 29 Day 1 (n=10)	-7.6 (± 10.1)			
Cycle 30 Day 1 (n=10)	-6.9 (± 8.4)			
Cycle 31 Day 1 (n=7)	-10.6 (± 10.4)			
Cycle 32 Day 1 (n=7)	-3.7 (± 10.1)			
Cycle 33 Day 1 (n=7)	-10 (± 14.1)			
End of treatment (n=1529)	-0.9 (± 11.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Systolic Blood Pressure at Specified Time Points

End point title	Change From Baseline in Systolic Blood Pressure at Specified Time Points[6]

End point description:

SAF, Here “N” (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category. In the below table 99999 represents as the sample size was not sufficient. Hence, Standard deviation was not calculated.

End point type	Primary

End point timeframe:

Baseline, Cycle 1 Days 1, 8, 15, 22; Cycle 2 Days 1, 8, 15; Cycle 3 to 33 (Day 1), and End of treatment

Notes:

[6] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=1096)	0.4 (± 10.8)			
Cycle 1 Day 8 (n=1896)	6.4 (± 15.9)			
Cycle 1 Day 15 (n=2149)	5.7 (± 16.3)			
Cycle 1 Day 22 (n=1579)	3.6 (± 15.7)			
Cycle 2 Day 1 (n=1978)	0.6 (± 14.6)			
Cycle 2 Day 8 (n=1343)	5.4 (± 15.9)			
Cycle 2 Day 15 (n=1724)	4.8 (± 16.5)			
Cycle 3 Day 1 (n=1413)	-1.1 (± 15.4)			

Cycle 4 Day 1 (n=959)	-0.9 (± 14.9)			
Cycle 5 Day 1 (n=674)	-1.3 (± 15.2)			
Cycle 6 Day 1 (n=527)	-1.1 (± 15.9)			
Cycle 7 Day 1 (n=374)	-0.5 (± 16)			
Cycle 8 Day 1 (n=297)	-1.6 (± 15.8)			
Cycle 9 Day 1 (n=248)	-0.7 (± 14.9)			
Cycle 10 Day 1 (n=197)	-0.9 (± 15.6)			
Cycle 11 Day 1 (n=163)	-1.2 (± 14.5)			
Cycle 12 Day 1 (n=143)	0.2 (± 15.3)			
Cycle 13 Day 1 (n=113)	1.1 (± 14.3)			
Cycle 14 Day 1 (n=92)	-1.1 (± 18.1)			
Cycle 15 Day 1 (n=78)	0.9 (± 14.5)			
Cycle 16 Day 1 (n=63)	-2.8 (± 14.2)			
Cycle 17 Day 1 (n=54)	1.1 (± 13.8)			
Cycle 18 Day 1 (n=44)	-1 (± 14.3)			
Cycle 19 Day 1 (n=37)	0.1 (± 19)			
Cycle 20 Day 1 (n=29)	4.6 (± 16.6)			
Cycle 21 Day 1 (n=24)	2.5 (± 15.8)			
Cycle 22 Day 1 (n=20)	2.7 (± 14)			
Cycle 23 Day 1 (n=16)	0.8 (± 10.5)			
Cycle 24 Day 1 (n=14)	5.9 (± 17.4)			
Cycle 25 Day 1 (n=14)	-0.2 (± 13.8)			
Cycle 26 Day 1 (n=13)	6.1 (± 21.1)			
Cycle 27 Day 1 (n=11)	2.3 (± 15.2)			
Cycle 28 Day 1 (n=11)	-2.7 (± 10.9)			
Cycle 29 Day 1 (n=10)	2.3 (± 16.6)			
Cycle 30 Day 1 (n=10)	4.0 (± 17.7)			
Cycle 31 Day 1 (n=7)	4.0 (± 13.2)			
Cycle 32 Day 1 (n=7)	9.3 (± 9.9)			
Cycle 33 Day 1 (n=7)	9.0 (± 13.7)			
End of treatment (n=1530)	-1.8 (± 16.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subject With Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at Specified Time Points

End point title	Percentage of Subject With Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at Specified Time Points[7]

End point description:

ECOG PS score was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death. SAF, Here “N” (number of subjects analyzed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

Baseline, Day 1 (Cycle 1 to 33), and End of treatment

Notes:

[7] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: percentage of subjects				
number (not applicable)				
Cycle 1 Day 1 (n=1553): Unchanged	89.4			
Cycle 1 Day 1 (n=1553): 0 to 1	6			
Cycle 1 Day 1 (n=1553): 0 to 2	0			
Cycle 1 Day 1 (n=1553): 0 to 3	0			
Cycle 1 Day 1 (n=1553): 0 to 4	0			
Cycle 1 Day 1 (n=1553): 1 to 0	4.3			
Cycle 1 Day 1 (n=1553): 1 to 2	0.3			
Cycle 1 Day 1 (n=1553): 1 to 3	0			
Cycle 1 Day 1 (n=1553): 1 to 4	0			
Cycle 1 Day 1 (n=1553): Missing	0.1			
Cycle 2 Day 1 (n=2298): Unchanged	71			
Cycle 2 Day 1 (n=2298): 0 to 1	16.6			
Cycle 2 Day 1 (n=2298): 0 to 2	1.3			
Cycle 2 Day 1 (n=2298): 0 to 3	0			
Cycle 2 Day 1 (n=2298): 0 to 4	0			
Cycle 2 Day 1 (n=2298): 1 to 0	5			
Cycle 2 Day 1 (n=2298): 1 to 2	5.4			
Cycle 2 Day 1 (n=2298): 1 to 3	0.4			
Cycle 2 Day 1 (n=2298): 1 to 4	0			
Cycle 2 Day 1 (n=2298): Missing	0.2			
Cycle 3 Day 1 (n=1616): Unchanged	69.8			
Cycle 3 Day 1 (n=1616): 0 to 1	19.5			
Cycle 3 Day 1 (n=1616): 0 to 2	0.9			
Cycle 3 Day 1 (n=1616): 0 to 3	0.2			
Cycle 3 Day 1 (n=1616): 0 to 4	0			
Cycle 3 Day 1 (n=1616): 1 to 0	5.3			
Cycle 3 Day 1 (n=1616): 1 to 2	4.1			
Cycle 3 Day 1 (n=1616): 1 to 3	0.1			
Cycle 3 Day 1 (n=1616): 1 to 4	0			
Cycle 3 Day 1 (n=1616): Missing	0.1			
Cycle 4 Day 1 (n=1098): Unchanged	69.9			
Cycle 4 Day 1 (n=1098): 0 to 1	17.8			
Cycle 4 Day 1 (n=1098): 0 to 2	1.3			
Cycle 4 Day 1 (n=1098): 0 to 3	0			
Cycle 4 Day 1 (n=1098): 0 to 4	0			
Cycle 4 Day 1 (n=1098): 1 to 0	5.9			
Cycle 4 Day 1 (n=1098): 1 to 2	4.6			
Cycle 4 Day 1 (n=1098): 1 to 3	0.5			
Cycle 4 Day 1 (n=1098): 1 to 4	0			

Cycle 4 Day 1 (n=1098): Missing	0.2			
Cycle 5 Day 1 (n=769): Unchanged	68.4			
Cycle 5 Day 1 (n=769): 0 to 1	19.4			
Cycle 5 Day 1 (n=769): 0 to 2	1.3			
Cycle 5 Day 1 (n=769): 0 to 3	0			
Cycle 5 Day 1 (n=769): 0 to 4	0			
Cycle 5 Day 1 (n=769): 1 to 0	6.5			
Cycle 5 Day 1 (n=769): 1 to 2	4.3			
Cycle 5 Day 1 (n=769): 1 to 3	0.1			
Cycle 5 Day 1 (n=769): 1 to 4	0			
Cycle 6 Day 1 (n=599): Unchanged	68.8			
Cycle 6 Day 1 (n=599): 0 to 1	20			
Cycle 6 Day 1 (n=599): 0 to 2	0.8			
Cycle 6 Day 1 (n=599): 0 to 3	0			
Cycle 6 Day 1 (n=599): 0 to 4	0			
Cycle 6 Day 1 (n=599): 1 to 0	5.3			
Cycle 6 Day 1 (n=599): 1 to 2	4.7			
Cycle 6 Day 1 (n=599): 1 to 3	0.2			
Cycle 6 Day 1 (n=599): 1 to 4	0			
Cycle 6 Day 1 (n=599): Missing	0.2			
Cycle 7 Day 1 (n=422): Unchanged	70.1			
Cycle 7 Day 1 (n=422): 0 to 1	20.1			
Cycle 7 Day 1 (n=422): 0 to 2	0.5			
Cycle 7 Day 1 (n=422): 0 to 3	0			
Cycle 7 Day 1 (n=422): 0 to 4	0			
Cycle 7 Day 1 (n=422): 1 to 0	5.7			
Cycle 7 Day 1 (n=422): 1 to 2	3.3			
Cycle 7 Day 1 (n=422): 1 to 3	0.2			
Cycle 7 Day 1 (n=422): 1 to 4	0			
Cycle 8 Day 1 (n=332): Unchanged	69.3			
Cycle 8 Day 1 (n=332): 0 to 1	21.4			
Cycle 8 Day 1 (n=332): 0 to 2	0.9			
Cycle 8 Day 1 (n=332): 0 to 3	0.3			
Cycle 8 Day 1 (n=332): 0 to 4	0			
Cycle 8 Day 1 (n=332): 1 to 0	6			
Cycle 8 Day 1 (n=332): 1 to 2	2.1			
Cycle 8 Day 1 (n=332): 1 to 3	0			
Cycle 8 Day 1 (n=332): 1 to 4	0			
Cycle 9 Day 1 (n=278): Unchanged	67.3			
Cycle 9 Day 1 (n=278): 0 to 1	22.7			
Cycle 9 Day 1 (n=278): 0 to 2	0.7			
Cycle 9 Day 1 (n=278): 0 to 3	0			
Cycle 9 Day 1 (n=278): 0 to 4	0			
Cycle 9 Day 1 (n=278): 1 to 0	7.2			
Cycle 9 Day 1 (n=278): 1 to 2	1.4			
Cycle 9 Day 1 (n=278): 1 to 3	0.4			
Cycle 9 Day 1 (n=278): 1 to 4	0			
Cycle 9 Day 1 (n=278): Missing	0.4			
Cycle 10 Day 1 (n=221): Unchanged	69.2			
Cycle 10 Day 1 (n=221): 0 to 1	21.3			
Cycle 10 Day 1 (n=221): 0 to 2	1.4			
Cycle 10 Day 1 (n=221): 0 to 3	0			

Cycle 10 Day 1 (n=221): 0 to 4	0			
Cycle 10 Day 1 (n=221): 1 to 0	6.3			
Cycle 10 Day 1 (n=221): 1 to 2	1.4			
Cycle 10 Day 1 (n=221): 1 to 3	0			
Cycle 10 Day 1 (n=221): 1 to 4	0			
Cycle 10 Day 1 (n=221): Missing	0.5			
Cycle 11 Day 1 (n=188): Unchanged	63.3			
Cycle 11 Day 1 (n=188): 0 to 1	23.4			
Cycle 11 Day 1 (n=188): 0 to 2	2.1			
Cycle 11 Day 1 (n=188): 0 to 3	0			
Cycle 11 Day 1 (n=188): 0 to 4	0			
Cycle 11 Day 1 (n=188): 1 to 0	8			
Cycle 11 Day 1 (n=188): 1 to 2	2.7			
Cycle 11 Day 1 (n=188): 1 to 3	0.5			
Cycle 11 Day 1 (n=188): 1 to 4	0			
Cycle 12 Day 1 (n=159): Unchanged	62.9			
Cycle 12 Day 1 (n=159): 0 to 1	25.8			
Cycle 12 Day 1 (n=159): 0 to 2	1.3			
Cycle 12 Day 1 (n=159): 0 to 3	0			
Cycle 12 Day 1 (n=159): 0 to 4	0			
Cycle 12 Day 1 (n=159): 1 to 0	6.3			
Cycle 12 Day 1 (n=159): 1 to 2	3.1			
Cycle 12 Day 1 (n=159): 1 to 3	0			
Cycle 12 Day 1 (n=159): 1 to 4	0			
Cycle 12 Day 1 (n=159): Missing	0.6			
Cycle 13 Day 1 (n=130): Unchanged	68.5			
Cycle 13 Day 1 (n=130): 0 to 1	22.3			
Cycle 13 Day 1 (n=130): 0 to 2	0.8			
Cycle 13 Day 1 (n=130): 0 to 3	0.8			
Cycle 13 Day 1 (n=130): 0 to 4	0			
Cycle 13 Day 1 (n=130): 1 to 0	5.4			
Cycle 13 Day 1 (n=130): 1 to 2	1.5			
Cycle 13 Day 1 (n=130): 1 to 3	0			
Cycle 13 Day 1 (n=130): 1 to 4	0			
Cycle 13 Day 1 (n=130): Missing	0.8			
Cycle 14 Day 1 (n=105): Unchanged	62.9			
Cycle 14 Day 1 (n=105): 0 to 1	27.6			
Cycle 14 Day 1 (n=105): 0 to 2	1.9			
Cycle 14 Day 1 (n=105): 0 to 3	0			
Cycle 14 Day 1 (n=105): 0 to 4	0			
Cycle 14 Day 1 (n=105): 1 to 0	5.7			
Cycle 14 Day 1 (n=105): 1 to 2	1			
Cycle 14 Day 1 (n=105): 1 to 3	0			
Cycle 14 Day 1 (n=105): 1 to 4	0			
Cycle 14 Day 1 (n=105): Missing	1			
Cycle 15 Day 1 (n=87): Unchanged	63.2			
Cycle 15 Day 1 (n=87): 0 to 1	26.4			
Cycle 15 Day 1 (n=87): 0 to 2	2.3			
Cycle 15 Day 1 (n=87): 0 to 3	0			
Cycle 15 Day 1 (n=87): 0 to 4	0			
Cycle 15 Day 1 (n=87): 1 to 0	6.9			
Cycle 15 Day 1 (n=87): 1 to 2	0			

Cycle 15 Day 1 (n=87): 1 to 3	0			
Cycle 15 Day 1 (n=87): 1 to 4	0			
Cycle 15 Day 1 (n=87): Missing	1.1			
Cycle 16 Day 1 (n=69): Unchanged	68.1			
Cycle 16 Day 1 (n=69): 0 to 1	21.7			
Cycle 16 Day 1 (n=69): 0 to 2	1.4			
Cycle 16 Day 1 (n=69): 0 to 3	0			
Cycle 16 Day 1 (n=69): 0 to 4	0			
Cycle 16 Day 1 (n=69): 1 to 0	5.8			
Cycle 16 Day 1 (n=69): 1 to 2	1.4			
Cycle 16 Day 1 (n=69): 1 to 3	0			
Cycle 16 Day 1 (n=69): 1 to 4	0			
Cycle 16 Day 1 (n=69): Missing	1.4			
Cycle 17 Day 1 (n=59): Unchanged	69.5			
Cycle 17 Day 1 (n=59): 0 to 1	20.3			
Cycle 17 Day 1 (n=59): 0 to 2	3.4			
Cycle 17 Day 1 (n=59): 0 to 3	0			
Cycle 17 Day 1 (n=59): 0 to 4	0			
Cycle 17 Day 1 (n=59): 1 to 0	5.1			
Cycle 17 Day 1 (n=59): 1 to 2	1.7			
Cycle 17 Day 1 (n=59): 1 to 3	0			
Cycle 17 Day 1 (n=59): 1 to 4	0			
Cycle 18 Day 1 (n=47): Unchanged	70.2			
Cycle 18 Day 1 (n=47): 0 to 1	17			
Cycle 18 Day 1 (n=47): 0 to 2	2.1			
Cycle 18 Day 1 (n=47): 0 to 3	0			
Cycle 18 Day 1 (n=47): 0 to 4	0			
Cycle 18 Day 1 (n=47): 1 to 0	8.5			
Cycle 18 Day 1 (n=47): 1 to 2	2.1			
Cycle 18 Day 1 (n=47): 1 to 3	0			
Cycle 18 Day 1 (n=47): 1 to 4	0			
Cycle 19 Day 1 (n=40): Unchanged	77.5			
Cycle 19 Day 1 (n=40): 0 to 1	15			
Cycle 19 Day 1 (n=40): 0 to 2	2.5			
Cycle 19 Day 1 (n=40): 0 to 3	0			
Cycle 19 Day 1 (n=40): 0 to 4	0			
Cycle 19 Day 1 (n=40): 1 to 0	5			
Cycle 19 Day 1 (n=40): 1 to 2	0			
Cycle 19 Day 1 (n=40): 1 to 3	0			
Cycle 19 Day 1 (n=40): 1 to 4	0			
Cycle 20 Day 1 (n=31): Unchanged	77.4			
Cycle 20 Day 1 (n=31): 0 to 1	16.1			
Cycle 20 Day 1 (n=31): 0 to 2	0			
Cycle 20 Day 1 (n=31): 0 to 3	0			
Cycle 20 Day 1 (n=31): 0 to 4	0			
Cycle 20 Day 1 (n=31): 1 to 0	6.5			
Cycle 20 Day 1 (n=31): 1 to 2	0			
Cycle 20 Day 1 (n=31): 1 to 3	0			
Cycle 20 Day 1 (n=31): 1 to 4	0			
Cycle 21 Day 1 (n=28): Unchanged	75			
Cycle 21 Day 1 (n=28): 0 to 1	17.9			
Cycle 21 Day 1 (n=28): 0 to 2	3.6			

Cycle 21 Day 1 (n=28): 0 to 3	0			
Cycle 21 Day 1 (n=28): 0 to 4	0			
Cycle 21 Day 1 (n=28): 1 to 0	3.6			
Cycle 21 Day 1 (n=28): 1 to 2	0			
Cycle 21 Day 1 (n=28): 1 to 3	0			
Cycle 21 Day 1 (n=28): 1 to 4	0			
Cycle 22 Day 1 (n=22): Unchanged	72.7			
Cycle 22 Day 1 (n=22): 0 to 1	18.2			
Cycle 22 Day 1 (n=22): 0 to 2	0			
Cycle 22 Day 1 (n=22): 0 to 3	0			
Cycle 22 Day 1 (n=22): 0 to 4	0			
Cycle 22 Day 1 (n=22): 1 to 0	4.5			
Cycle 22 Day 1 (n=22): 1 to 2	4.5			
Cycle 22 Day 1 (n=22): 1 to 3	0			
Cycle 22 Day 1 (n=22): 1 to 4	0			
Cycle 23 Day 1 (n=17): Unchanged	70.6			
Cycle 23 Day 1 (n=17): 0 to 1	23.5			
Cycle 23 Day 1 (n=17): 0 to 2	0			
Cycle 23 Day 1 (n=17): 0 to 3	0			
Cycle 23 Day 1 (n=17): 0 to 4	0			
Cycle 23 Day 1 (n=17): 1 to 0	5.9			
Cycle 23 Day 1 (n=17): 1 to 2	0			
Cycle 23 Day 1 (n=17): 1 to 3	0			
Cycle 23 Day 1 (n=17): 1 to 4	0			
Cycle 24 Day 1 (n=15): Unchanged	73.3			
Cycle 24 Day 1 (n=15): 0 to 1	26.7			
Cycle 24 Day 1 (n=15): 0 to 2	0			
Cycle 24 Day 1 (n=15): 0 to 3	0			
Cycle 24 Day 1 (n=15): 0 to 4	0			
Cycle 24 Day 1 (n=15): 1 to 0	0			
Cycle 24 Day 1 (n=15): 1 to 2	0			
Cycle 24 Day 1 (n=15): 1 to 3	0			
Cycle 24 Day 1 (n=15): 1 to 4	0			
Cycle 25 Day 1 (n=14): Unchanged	71.4			
Cycle 25 Day 1 (n=14): 0 to 1	21.4			
Cycle 25 Day 1 (n=14): 0 to 2	0			
Cycle 25 Day 1 (n=14): 0 to 3	0			
Cycle 25 Day 1 (n=14): 0 to 4	0			
Cycle 25 Day 1 (n=14): 1 to 0	7.1			
Cycle 25 Day 1 (n=14): 1 to 2	0			
Cycle 25 Day 1 (n=14): 1 to 3	0			
Cycle 25 Day 1 (n=14): 1 to 4	0			
Cycle 26 Day 1 (n=14): Unchanged	64.3			
Cycle 26 Day 1 (n=14): 0 to 1	28.6			
Cycle 26 Day 1 (n=14): 0 to 2	0			
Cycle 26 Day 1 (n=14): 0 to 3	0			
Cycle 26 Day 1 (n=14): 0 to 4	0			
Cycle 26 Day 1 (n=14): 1 to 0	0			
Cycle 26 Day 1 (n=14): 1 to 2	0			
Cycle 26 Day 1 (n=14): 1 to 3	7.1			
Cycle 26 Day 1 (n=14): 1 to 4	0			
Cycle 27 Day 1 (n=12): Unchanged	66.7			

Cycle 27 Day 1 (n=12): 0 to 1	33.3			
Cycle 27 Day 1 (n=12): 0 to 2	0			
Cycle 27 Day 1 (n=12): 0 to 3	0			
Cycle 27 Day 1 (n=12): 0 to 4	0			
Cycle 27 Day 1 (n=12): 1 to 0	0			
Cycle 27 Day 1 (n=12): 1 to 2	0			
Cycle 27 Day 1 (n=12): 1 to 3	0			
Cycle 27 Day 1 (n=12): 1 to 4	0			
Cycle 28 Day 1 (n=12): Unchanged	58.3			
Cycle 28 Day 1 (n=12): 0 to 1	41.7			
Cycle 28 Day 1 (n=12): 0 to 2	0			
Cycle 28 Day 1 (n=12): 0 to 3	0			
Cycle 28 Day 1 (n=12): 0 to 4	0			
Cycle 28 Day 1 (n=12): 1 to 0	0			
Cycle 28 Day 1 (n=12): 1 to 2	0			
Cycle 28 Day 1 (n=12): 1 to 3	0			
Cycle 28 Day 1 (n=12): 1 to 4	0			
Cycle 29 Day 1 (n=10): Unchanged	50			
Cycle 29 Day 1 (n=10): 0 to 1	50			
Cycle 29 Day 1 (n=10): 0 to 2	0			
Cycle 29 Day 1 (n=10): 0 to 3	0			
Cycle 29 Day 1 (n=10): 0 to 4	0			
Cycle 29 Day 1 (n=10): 1 to 0	0			
Cycle 29 Day 1 (n=10): 1 to 2	0			
Cycle 29 Day 1 (n=10): 1 to 3	0			
Cycle 29 Day 1 (n=10): 1 to 4	0			
Cycle 30 Day 1 (n=10): Unchanged	50			
Cycle 30 Day 1 (n=10): 0 to 1	50			
Cycle 30 Day 1 (n=10): 0 to 2	0			
Cycle 30 Day 1 (n=10): 0 to 3	0			
Cycle 30 Day 1 (n=10): 0 to 4	0			
Cycle 30 Day 1 (n=10): 1 to 0	0			
Cycle 30 Day 1 (n=10): 1 to 2	0			
Cycle 30 Day 1 (n=10): 1 to 3	0			
Cycle 30 Day 1 (n=10): 1 to 4	0			
Cycle 31 Day 1 (n=7): Unchanged	57.1			
Cycle 31 Day 1 (n=7): 0 to 1	42.9			
Cycle 31 Day 1 (n=7): 0 to 2	0			
Cycle 31 Day 1 (n=7): 0 to 3	0			
Cycle 31 Day 1 (n=7): 0 to 4	0			
Cycle 31 Day 1 (n=7): 1 to 0	0			
Cycle 31 Day 1 (n=7): 1 to 2	0			
Cycle 31 Day 1 (n=7): 1 to 3	0			
Cycle 31 Day 1 (n=7): 1 to 4	0			
Cycle 32 Day 1 (n=7): Unchanged	42.9			
Cycle 32 Day 1 (n=7): 0 to 1	57.1			
Cycle 32 Day 1 (n=7): 0 to 2	0			
Cycle 32 Day 1 (n=7): 0 to 3	0			
Cycle 32 Day 1 (n=7): 0 to 4	0			
Cycle 32 Day 1 (n=7): 1 to 0	0			
Cycle 32 Day 1 (n=7): 1 to 2	0			
Cycle 32 Day 1 (n=7): 1 to 3	0			

Cycle 32 Day 1 (n=7): 1 to 4	0			
Cycle 33 Day 1 (n=6): Unchanged	33.3			
Cycle 33 Day 1 (n=6): 0 to 1	66.7			
Cycle 33 Day 1 (n=6): 0 to 2	0			
Cycle 33 Day 1 (n=6): 0 to 3	0			
Cycle 33 Day 1 (n=6): 0 to 4	0			
Cycle 33 Day 1 (n=6): 1 to 0	0			
Cycle 33 Day 1 (n=6): 1 to 2	0			
Cycle 33 Day 1 (n=6): 1 to 3	0			
Cycle 33 Day 1 (n=6): 1 to 4	0			
End of treatment (n=1855): Unchanged	43.5			
End of treatment (n=1855): 0 to 1	21.7			
End of treatment (n=1855): 0 to 2	7			
End of treatment (n=1855): 0 to 3	2.4			
End of treatment (n=1855): 0 to 4	0.2			
End of treatment (n=1855): 1 to 0	2.2			
End of treatment (n=1855): 1 to 2	13.5			
End of treatment (n=1855): 1 to 3	8.6			
End of treatment (n=1855): 1 to 4	0.8			
End of treatment (n=1855): Missing	0.2			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Number of Cycles Completed

End point title	Extent of Exposure - Number of Cycles Completed[8]

End point description:

SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[8] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2862			
Units: cycles				
arithmetic mean (standard deviation)	4.1 (± 4.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Treatment Duration in Weeks

End point title	Extent of Exposure - Treatment Duration in Weeks[9]

End point description:

Overall treatment duration in weeks including interruptions/delays and drug holidays was calculated as (Day of last dose minus day of first dose + 1) / 7. SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[9] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: weeks				
arithmetic mean (standard deviation)	15.6 (± 18.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Treatment Duration for Actual Weeks Study Drug Received

End point title	Extent of Exposure - Treatment Duration for Actual Weeks Study Drug Received[10]

End point description:

Actual treatment duration in weeks excluding interruptions/delays and drug holidays was calculated as (Day of last dose minus day of first dose + 1) minus days of interruption and drug holidays / 7. SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[10] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2864			
Units: weeks				
arithmetic mean (standard deviation)	11.2 (± 12.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Actual Daily Dose of Regorafenib

End point title	Extent of Exposure - Actual Daily Dose of Regorafenib[11]

End point description:

SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[11] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2862			
Units: milligram (mg)				
arithmetic mean (standard deviation)	145.8 (± 19.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Percent of Planned Dose Received

End point title	Extent of Exposure - Percent of Planned Dose Received[12]

End point description:

Planned dose describes the intended initial dose of the study drug. SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[12] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2862			
Units: percent of planned dose				
arithmetic mean (standard deviation)	75.1 (± 19.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Extent of Exposure - Percentage of Subjects With Total Amount of Dose Including Categories

End point title	Extent of Exposure - Percentage of Subjects With Total Amount of Dose Including Categories[13]

End point description:

SAF, number of subjects analysed signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[13] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2862			
Units: percentage of subjects				
number (not applicable)				
=<2000 mg	7.9			
>2000 to 5000 mg	21.6			
>5000 to 8000 mg	23.2			
>8000 to 11000 mg	16.2			
>11000 to 14000 mg	8.9			
>14000 mg	22.2			
Missing	0.1			

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[14]

End point description:

Progression-free survival was defined as the time from date of treatment assignment (i.e. date of first treatment) to date of first observed disease progression or death due to any cause, if death occurred while the subject was in the study (that is, by the last visit including during the safety follow-up visit date) and before progression was observed. Tumor measurements were made at intervals and with methods that complied with the institution’s best standard of care. Full analysis set (FAS) included all subjects who were assigned to treatment.

End point type	Primary

End point timeframe:

From start of study treatment until 33 months

Notes:

[14] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Regorafenib (BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	2872			
Units: days				
median (confidence interval 95%)	82 (79 to 83)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of study treatment up to 30 days after the last dose of study drug	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Regorafenib (BAY73-4506)
Reporting group description:	
Subjects received regorafenib 160 mg (4 x 40 mg tablets) per oral once daily for 3 weeks of every 4 week cycle (that is 3 weeks on, 1 week off).	

Serious adverse events	Regorafenib (BAY73-4506)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1253 / 2864 (43.75%)		
number of deaths (all causes)	547		
number of deaths resulting from adverse events	407		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Malignant ascites			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Malignant pleural effusion			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Sarcoma			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to meninges			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Tumour associated fever			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer metastatic			

subjects affected / exposed	11 / 2864 (0.38%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 10			
Infected neoplasm				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cancer pain				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Colorectal cancer				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 5			
Tumour perforation				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Tumour fistulisation				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Bleeding varicose vein				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				

subjects affected / exposed	6 / 2864 (0.21%)			
occurrences causally related to treatment / all	16 / 18			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lymphoedema				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Superior vena cava syndrome				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Haemodynamic instability			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 2864 (0.84%)		
occurrences causally related to treatment / all	15 / 35		
deaths causally related to treatment / all	1 / 4		
Chest pain			
subjects affected / exposed	9 / 2864 (0.31%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Chronic fatigue syndrome			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	1 / 8		
Fatigue			
subjects affected / exposed	20 / 2864 (0.70%)		
occurrences causally related to treatment / all	14 / 21		
deaths causally related to treatment / all	0 / 0		

Gait disturbance				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	66 / 2864 (2.30%)			
occurrences causally related to treatment / all	17 / 76			
deaths causally related to treatment / all	0 / 1			
Sudden death				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Performance status decreased			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 2		
General physical health deterioration			
subjects affected / exposed	288 / 2864 (10.06%)		
occurrences causally related to treatment / all	15 / 433		
deaths causally related to treatment / all	2 / 213		
Inflammation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 5		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Metrorrhagia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Prostatic obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Female genital tract fistula			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Adnexal torsion			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		

Aspiration			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Atelectasis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bronchial obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catarrh			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	35 / 2864 (1.22%)		
occurrences causally related to treatment / all	1 / 53		
deaths causally related to treatment / all	0 / 12		
Dyspnoea exertional			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epistaxis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			

subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 1			
Hiccups				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Lung disorder				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	26 / 2864 (0.91%)			
occurrences causally related to treatment / all	0 / 33			
deaths causally related to treatment / all	0 / 3			
Pleuritic pain				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pneumothorax				
subjects affected / exposed	9 / 2864 (0.31%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 1			
Pneumothorax spontaneous				

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	18 / 2864 (0.63%)			
occurrences causally related to treatment / all	7 / 21			
deaths causally related to treatment / all	1 / 1			
Pulmonary oedema				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	14 / 2864 (0.49%)			
occurrences causally related to treatment / all	0 / 22			
deaths causally related to treatment / all	0 / 12			
Pharyngeal inflammation				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	11 / 2864 (0.38%)			
occurrences causally related to treatment / all	1 / 12			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Depression				

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mental status changes				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
Psychotic disorder				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device breakage				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device leakage				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	6 / 8			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase				

increased				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	21 / 2864 (0.73%)			
occurrences causally related to treatment / all	4 / 31			
deaths causally related to treatment / all	0 / 1			
Electrocardiogram QT prolonged				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood urine present				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anticoagulation drug level above therapeutic				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coagulation test abnormal				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Eastern Cooperative Oncology Group performance status worsened				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Concussion				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cystitis radiation				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Femoral neck fracture			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suture rupture			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Traumatic haemothorax				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stoma site haemorrhage				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Angina pectoris				

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	9 / 2864 (0.31%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac failure acute			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	1 / 7		
Myocardial infarction			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Apraxia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	1 / 2			
Cerebral ischaemia				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cervical cord compression				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma hepatic			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Dizziness			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysaesthesia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 2		
Horner's syndrome			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Monoparesis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neuralgia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral motor neuropathy			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Somnolence			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Vocal cord paralysis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vocal cord paresis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical radiculopathy			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haematoma			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures with secondary generalisation			

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial mass				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	15 / 2864 (0.52%)			
occurrences causally related to treatment / all	8 / 23			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemolysis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemolytic anaemia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	16 / 17		
deaths causally related to treatment / all	0 / 0		
Thrombotic microangiopathy			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperprothrombinaemia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vascular occlusion			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal vein thrombosis			

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcerative keratitis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	57 / 2864 (1.99%)			
occurrences causally related to treatment / all	2 / 68			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	7 / 2864 (0.24%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	24 / 2864 (0.84%)			
occurrences causally related to treatment / all	0 / 31			
deaths causally related to treatment / all	0 / 4			
Colitis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis ulcerative				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic fistula			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 1		
Constipation			
subjects affected / exposed	13 / 2864 (0.45%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	28 / 2864 (0.98%)		
occurrences causally related to treatment / all	26 / 33		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Enteritis			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastric perforation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis alcoholic			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 1		
Haematemesis			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 1		
Ileus paralytic			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal fistula			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	33 / 2864 (1.15%)		
occurrences causally related to treatment / all	1 / 43		
deaths causally related to treatment / all	0 / 6		
Intestinal perforation			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	3 / 9		
deaths causally related to treatment / all	1 / 2		
Jejunal perforation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			

subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 1			
Mallory-Weiss syndrome				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	9 / 2864 (0.31%)			
occurrences causally related to treatment / all	3 / 10			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal haemorrhage				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Proctitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	10 / 2864 (0.35%)		
occurrences causally related to treatment / all	2 / 12		
deaths causally related to treatment / all	0 / 1		
Rectal perforation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	28 / 2864 (0.98%)		
occurrences causally related to treatment / all	1 / 35		
deaths causally related to treatment / all	0 / 2		
Small intestinal perforation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			

subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	19 / 2864 (0.66%)			
occurrences causally related to treatment / all	10 / 21			
deaths causally related to treatment / all	0 / 0			
Anal haemorrhage				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	11 / 2864 (0.38%)			
occurrences causally related to treatment / all	1 / 13			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocutaneous fistula				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumatosis intestinalis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric stenosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	12 / 2864 (0.42%)		
occurrences causally related to treatment / all	0 / 16		
deaths causally related to treatment / all	0 / 4		
Enterovesical fistula			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Rectal obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula of small intestine			

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia perforation				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	12 / 2864 (0.42%)			
occurrences causally related to treatment / all	1 / 12			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 1			
Cholecystitis acute				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	6 / 2864 (0.21%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 2			
Hepatic failure				

subjects affected / exposed	29 / 2864 (1.01%)		
occurrences causally related to treatment / all	0 / 48		
deaths causally related to treatment / all	0 / 19		
Hepatic function abnormal			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic pain			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	7 / 14		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Perforation bile duct			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct stenosis			

subjects affected / exposed	12 / 2864 (0.42%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	14 / 2864 (0.49%)			
occurrences causally related to treatment / all	4 / 18			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermal cyst				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis acneiform				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis allergic				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity vasculitis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	10 / 2864 (0.35%)		
occurrences causally related to treatment / all	12 / 13		
deaths causally related to treatment / all	0 / 0		
Rash macular			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	12 / 2864 (0.42%)		
occurrences causally related to treatment / all	16 / 16		
deaths causally related to treatment / all	0 / 0		
Rash vesicular			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Skin ulcer haemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic skin eruption			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin toxicity			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 3		
Ureteric obstruction			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Ureteric stenosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Urinary bladder polyp			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal injury			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Urinary tract obstruction			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	20 / 2864 (0.70%)		
occurrences causally related to treatment / all	4 / 24		
deaths causally related to treatment / all	0 / 3		
Prerenal failure			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid disorder			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	26 / 2864 (0.91%)		
occurrences causally related to treatment / all	0 / 32		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			

subjects affected / exposed	6 / 2864 (0.21%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haematoma muscle				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis of jaw				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fournier's gangrene			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Herpes simplex otitis externa			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	9 / 2864 (0.31%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Liver abscess			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Necrotising fasciitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orchitis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Peritonitis			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	36 / 2864 (1.26%)		
occurrences causally related to treatment / all	3 / 48		
deaths causally related to treatment / all	0 / 8		
Pneumonia chlamydial			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia streptococcal			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal abscess			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salmonellosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	21 / 2864 (0.73%)		
occurrences causally related to treatment / all	4 / 28		
deaths causally related to treatment / all	1 / 8		
Septic shock			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Upper respiratory tract infection			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	17 / 2864 (0.59%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal abscess			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal sepsis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle abscess			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fungal oesophagitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess soft tissue			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal fistula infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Febrile infection			

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterococcal sepsis			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Clostridium difficile infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Psoas abscess			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal infection			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection pseudomonal			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bacterial pyelonephritis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	9 / 2864 (0.31%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 2		
Anorectal infection			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scrotal infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Biliary abscess			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Wound infection bacterial			

subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sphingomonas paucimobilis infection				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infected fistula				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspergillus infection				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia pyelonephritis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	24 / 2864 (0.84%)		
occurrences causally related to treatment / all	8 / 27		
deaths causally related to treatment / all	0 / 1		
Failure to thrive			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Hyperglycaemia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	11 / 12		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Steroid diabetes			
subjects affected / exposed	1 / 2864 (0.03%)		
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	Regorafenib (BAY73-4506)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2767 / 2864 (96.61%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	982 / 2864 (34.29%)		
occurrences (all)	2517		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	610 / 2864 (21.30%)		
occurrences (all)	1159		
Fatigue			
subjects affected / exposed	1181 / 2864 (41.24%)		
occurrences (all)	2126		
Mucosal inflammation			
subjects affected / exposed	409 / 2864 (14.28%)		
occurrences (all)	628		
Pyrexia			
subjects affected / exposed	545 / 2864 (19.03%)		
occurrences (all)	733		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	228 / 2864 (7.96%)		
occurrences (all)	269		
Dysphonia			
subjects affected / exposed	764 / 2864 (26.68%)		
occurrences (all)	959		
Dyspnoea			
subjects affected / exposed	350 / 2864 (12.22%)		
occurrences (all)	452		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	262 / 2864 (9.15%)		
occurrences (all)	486		

Aspartate aminotransferase increased				
subjects affected / exposed	335 / 2864 (11.70%)			
occurrences (all)	572			
Blood bilirubin increased				
subjects affected / exposed	452 / 2864 (15.78%)			
occurrences (all)	958			
Lipase increased				
subjects affected / exposed	237 / 2864 (8.28%)			
occurrences (all)	514			
Weight decreased				
subjects affected / exposed	875 / 2864 (30.55%)			
occurrences (all)	1140			
Blood alkaline phosphatase increased				
subjects affected / exposed	191 / 2864 (6.67%)			
occurrences (all)	257			
Nervous system disorders				
Headache				
subjects affected / exposed	294 / 2864 (10.27%)			
occurrences (all)	380			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	295 / 2864 (10.30%)			
occurrences (all)	570			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	509 / 2864 (17.77%)			
occurrences (all)	712			
Abdominal pain upper				
subjects affected / exposed	169 / 2864 (5.90%)			
occurrences (all)	220			
Constipation				
subjects affected / exposed	496 / 2864 (17.32%)			
occurrences (all)	602			
Diarrhoea				

subjects affected / exposed	907 / 2864 (31.67%)			
occurrences (all)	1857			
Dry mouth				
subjects affected / exposed	147 / 2864 (5.13%)			
occurrences (all)	166			
Nausea				
subjects affected / exposed	480 / 2864 (16.76%)			
occurrences (all)	632			
Stomatitis				
subjects affected / exposed	360 / 2864 (12.57%)			
occurrences (all)	505			
Vomiting				
subjects affected / exposed	376 / 2864 (13.13%)			
occurrences (all)	517			
Skin and subcutaneous tissue disorders				
Dry skin				
subjects affected / exposed	149 / 2864 (5.20%)			
occurrences (all)	185			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1230 / 2864 (42.95%)			
occurrences (all)	3218			
Rash				
subjects affected / exposed	353 / 2864 (12.33%)			
occurrences (all)	488			
Renal and urinary disorders				
Proteinuria				
subjects affected / exposed	262 / 2864 (9.15%)			
occurrences (all)	435			
Endocrine disorders				
Hypothyroidism				
subjects affected / exposed	147 / 2864 (5.13%)			
occurrences (all)	173			
Musculoskeletal and connective tissue disorders				

Arthralgia			
subjects affected / exposed	198 / 2864 (6.91%)		
occurrences (all)	248		
Back pain			
subjects affected / exposed	320 / 2864 (11.17%)		
occurrences (all)	433		
Myalgia			
subjects affected / exposed	195 / 2864 (6.81%)		
occurrences (all)	236		
Pain in extremity			
subjects affected / exposed	152 / 2864 (5.31%)		
occurrences (all)	225		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	186 / 2864 (6.49%)		
occurrences (all)	227		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	190 / 2864 (6.63%)		
occurrences (all)	282		
Hypophosphataemia			
subjects affected / exposed	320 / 2864 (11.17%)		
occurrences (all)	768		
Decreased appetite			
subjects affected / exposed	1000 / 2864 (34.92%)		
occurrences (all)	1411		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	1. Inclusion criteria concerning previous therapy for KRAS unknown subjects and acceptable limits for total bilirubin in subjects with documented Gilbert's Syndrome were made consistent with the preceding CORRECT trial to avoid uncertainty among the investigators. 2. Introduction of a more flexible and individualized schedule of liver function monitoring during treatment, where alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin must be monitored closely, at least every two weeks during the first 2 cycles of treatment. 3. Addition of a time window for coagulation measurements on Day 1 of Cycle 1. 4. Determination of a timeframe for blood and urine sample collection prior to dosing, during treatment phase. 5. Changes to make the text consistent with the eCRF concerning demographic and baseline characteristics, and with other study documents (Study Drug Reconciliation and Destruction Log, interactive voice response system (IVRS)/interactive web response system (IWRS) site manual).
17 September 2012	1. Modification in the wording of the inclusion criterion concerning KRAS negative or unknown subjects, allowing the inclusion of subjects who have not received prior therapy with bevacizumab and cetuximab / panitumumab. 2. Clarification about the planning of subgroup analyses for Mexican and Russian populations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported