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

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

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	02 January 2015

Results information

Result version number	v1
This version publication date	02 July 2016
First version publication date	02 July 2016

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 HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	02 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2015
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 02 January 2015 (data cut-off date).

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 2851 subjects had terminated treatment at the time of the data cut-off.

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
Safety follow-up completed	1589 [1]
Completed	2851
Not completed	21
Study drug never administered	8
On-going	13

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: In this study only 1589 subjects completed the safety follow-up 30 days after the last dose of the study. However, this is not a criteria for completing the study. Therefore the number of subjects who completed the study are higher than those who completed the safety follow-up.

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	1251			
TEAEs leading to discontinuation of drug	720			
Drug related TEAEs	2613			
Subjects who died (Grade 5 TEAEs)	404			

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)	23.5			
Prothrombin Intl. Normalized Ratio (n=1719)	20.9			
Prothrombin Time (n=684)	29.2			
Alanine Aminotransferase (n=2049)	43.9			
Alkaline Phosphatase (n=993)	48.5			
Aspartate Aminotransferase (n=1630)	61.4			
Bilirubin (n=2290)	58.1			
Calcium (n=2266)	3.5			
Chloride (n=2225)	11.2			
Creatinine (n=2240)	12.9			
Direct Bilirubin (n=1368)	61.9			
Phosphate (n=2111)	3.8			
Potassium (n=2312)	13.4			
Sodium (n=2392)	5			

Triacylglycerol Lipase (n=2138)	37.6			
Basophils (n=1878)	5.6			
Basophils/Leukocytes (n=695)	8.2			
Eosinophils (n=1773)	13.7			
Eosinophils/Leukocytes (n=642)	20.7			
Erythrocytes (n=2374)	10.3			
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)	38.1			
Neutrophils/Leukocytes (n=507)	49.7			
Platelets (n=2215)	15.4			
Thyrotropin (n=1805)	36.3			
Thyroxine, Free (n=1611)	9.8			
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)	7.8			
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)	29.9			
Creatinine (n=2149)	23.8			
Direct Bilirubin (n=1736)	0.2			
Phosphate (n=2009)	69.1			
Potassium (n=2312)	27.7			
Sodium (n=2220)	36			
Triacylglycerol Lipase (n=2150)	7			
Basophils (n=1879)	2.4			
Basophils/Leukocytes (n=701)	2			
Eosinophils (n=1849)	10.3			
Eosinophils/Leukocytes (n=636)	18.9			
Erythrocytes (n=1351)	39.5			
Hematocrit (n=1360)	47.9			
Hemoglobin (n=1262)	44.9			
Leukocytes (n=2343)	13.2			
Lymphocytes (n=1388)	39.1			
Lymphocytes/Leukocytes (n=369)	56.1			
Monocytes (n=1920)	3.8			
Monocytes/Leukocytes (n=714)	7.4			
Neutrophils (n=1968)	5.9			
Neutrophils/Leukocytes (n=714)	3.8			
Platelets (n=2169)	30.1			
Thyrotropin (n=1926)	4.8			
Thyroxine, Free (n=1644)	4.9			
Triiodothyronine, Free (n=1285)	18.6			

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	2864			
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 19 Day 1 (n = 36)	1.2 (± 13.2)			
Cycle 20 Day 1 (n = 28)	3.7 (± 14.3)			
Cycle 21 Day 1 (n = 24)	3.9 (± 14.3)			
Cycle 22 Day 1 (n = 18)	2.7 (± 9.8)			
Cycle 23 Day 1 (n = 15)	-0.9 (± 13.4)			
Cycle 24 Day 1 (n = 11)	-1.4 (± 11)			
Cycle 25 Day 1 (n = 11)	0.9 (± 12.6)			
Cycle 26 Day 1 (n = 9)	2.6 (± 14.4)			
Cycle 27 Day 1 (n = 7)	-3 (± 11.3)			
Cycle 28 Day 1 (n = 7)	1.4 (± 14.5)			
Cycle 29 Day 1 (n = 5)	-4.6 (± 12.2)			
Cycle 30 Day 1 (n = 3)	-7.7 (± 14.2)			
Cycle 31 Day 1 (n = 1)	7 (± 99999)			
Cycle 32 Day 1 (n = 1)	3 (± 99999)			
Cycle 33 Day 1 (n = 1)	-1 (± 99999)			
End of Treatment (n = 1468)	4.5 (± 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=36)	-3.5 (± 12.2)			
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=18)	-4.9 (± 13)			
Cycle 23 Day 1 (n=15)	-4.4 (± 10.6)			
Cycle 24 Day 1 (n=11)	-3.1 (± 12.1)			
Cycle 25 Day 1 (n=11)	-6.7 (± 13)			
Cycle 26 Day 1 (n=9)	-5.2 (± 9.5)			
Cycle 27 Day 1 (n=7)	-3.6 (± 11)			
Cycle 28 Day 1 (n=7)	-3.9 (± 13.2)			
Cycle 29 Day 1 (n=5)	-5.2 (± 10.4)			
Cycle 30 Day 1 (n=3)	-3.3 (± 7.6)			
Cycle 31 Day 1 (n=1)	6 (± 99999)			
Cycle 32 Day 1 (n=1)	6 (± 99999)			
Cycle 33 Day 1 (n=1)	4 (± 99999)			
End of Treatment (n=1520)	-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	2841			
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 (± 4.6)			
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=36)	0.1 (± 19.3)			
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=18)	1.9 (± 14.6)			
Cycle 23 Day 1 (n=15)	0.1 (± 10.5)			
Cycle 24 Day 1 (n=11)	3.5 (± 19)			
Cycle 25 Day 1 (n=11)	-1.6 (± 14.2)			
Cycle 26 Day 1 (n=9)	6.8 (± 25)			
Cycle 27 Day 1 (n=7)	1.4 (± 18.4)			
Cycle 28 Day 1 (n=7)	-0.3 (± 13.3)			
Cycle 29 Day 1 (n=5)	-2.2 (± 19.5)			
Cycle 30 Day 1 (n=3)	3 (± 11.5)			
Cycle 31 Day 1 (n=1)	6 (± 99999)			
Cycle 32 Day 1 (n=1)	11 (± 99999)			
Cycle 33 Day 1 (n=1)	20 (± 99999)			
End of Treatment (n=1521)	-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=39): Unchanged	76.9			
Cycle 19 Day 1 (n=39): 0 to 1	15.4			
Cycle 19 Day 1 (n=39): 0 to 2	2.6			
Cycle 19 Day 1 (n=39): 0 to 3	0			
Cycle 19 Day 1 (n=39): 0 to 4	0			
Cycle 19 Day 1 (n=39): 1 to 0	5.1			
Cycle 19 Day 1 (n=39): 1 to 2	0			
Cycle 19 Day 1 (n=39): 1 to 3	0			
Cycle 19 Day 1 (n=39): 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=20): Unchanged	75			
Cycle 22 Day 1 (n=20): 0 to 1	20			
Cycle 22 Day 1 (n=20): 0 to 2	0			
Cycle 22 Day 1 (n=20): 0 to 3	0			
Cycle 22 Day 1 (n=20): 0 to 4	0			
Cycle 22 Day 1 (n=20): 1 to 0	5			
Cycle 22 Day 1 (n=20): 1 to 2	0			
Cycle 22 Day 1 (n=20): 1 to 3	0			
Cycle 22 Day 1 (n=20): 1 to 4	0			
Cycle 23 Day 1 (n=16): Unchanged	68.8			
Cycle 23 Day 1 (n=16): 0 to 1	25			
Cycle 23 Day 1 (n=16): 0 to 2	0			
Cycle 23 Day 1 (n=16): 0 to 3	0			
Cycle 23 Day 1 (n=16): 0 to 4	0			
Cycle 23 Day 1 (n=16): 1 to 0	6.3			
Cycle 23 Day 1 (n=16): 1 to 2	0			
Cycle 23 Day 1 (n=16): 1 to 3	0			
Cycle 23 Day 1 (n=16): 1 to 4	0			
Cycle 24 Day 1 (n=12): Unchanged	75			
Cycle 24 Day 1 (n=12): 0 to 1	25			
Cycle 24 Day 1 (n=12): 0 to 2	0			
Cycle 24 Day 1 (n=12): 0 to 3	0			
Cycle 24 Day 1 (n=12): 0 to 4	0			
Cycle 24 Day 1 (n=12): 1 to 0	0			
Cycle 24 Day 1 (n=12): 1 to 2	0			
Cycle 24 Day 1 (n=12): 1 to 3	0			
Cycle 24 Day 1 (n=12): 1 to 4	0			
Cycle 25 Day 1 (n=11): Unchanged	72.7			
Cycle 25 Day 1 (n=11): 0 to 1	18.2			
Cycle 25 Day 1 (n=11): 0 to 2	0			
Cycle 25 Day 1 (n=11): 0 to 3	0			
Cycle 25 Day 1 (n=11): 0 to 4	0			
Cycle 25 Day 1 (n=11): 1 to 0	9.1			
Cycle 25 Day 1 (n=11): 1 to 2	0			
Cycle 25 Day 1 (n=11): 1 to 3	0			
Cycle 25 Day 1 (n=11): 1 to 4	0			
Cycle 26 Day 1 (n=10): Unchanged	60			
Cycle 26 Day 1 (n=10): 0 to 1	30			
Cycle 26 Day 1 (n=10): 0 to 2	0			
Cycle 26 Day 1 (n=10): 0 to 3	0			
Cycle 26 Day 1 (n=10): 0 to 4	0			
Cycle 26 Day 1 (n=10): 1 to 0	0			
Cycle 26 Day 1 (n=10): 1 to 2	0			
Cycle 26 Day 1 (n=10): 1 to 3	10			
Cycle 26 Day 1 (n=10): 1 to 4	0			
Cycle 27 Day 1 (n=8): Unchanged	62.5			

Cycle 27 Day 1 (n=8): 0 to 1	37.5			
Cycle 27 Day 1 (n=8): 0 to 2	0			
Cycle 27 Day 1 (n=8): 0 to 3	0			
Cycle 27 Day 1 (n=8): 0 to 4	0			
Cycle 27 Day 1 (n=8): 1 to 0	0			
Cycle 27 Day 1 (n=8): 1 to 2	0			
Cycle 27 Day 1 (n=8): 1 to 3	0			
Cycle 27 Day 1 (n=8): 1 to 4	0			
Cycle 28 Day 1 (n=8): Unchanged	50			
Cycle 28 Day 1 (n=8): 0 to 1	50			
Cycle 28 Day 1 (n=8): 0 to 2	0			
Cycle 28 Day 1 (n=8): 0 to 3	0			
Cycle 28 Day 1 (n=8): 0 to 4	0			
Cycle 28 Day 1 (n=8): 1 to 0	0			
Cycle 28 Day 1 (n=8): 1 to 2	0			
Cycle 28 Day 1 (n=8): 1 to 3	0			
Cycle 28 Day 1 (n=8): 1 to 4	0			
Cycle 29 Day 1 (n=5): Unchanged	20			
Cycle 29 Day 1 (n=5): 0 to 1	80			
Cycle 29 Day 1 (n=5): 0 to 2	0			
Cycle 29 Day 1 (n=5): 0 to 3	0			
Cycle 29 Day 1 (n=5): 0 to 4	0			
Cycle 29 Day 1 (n=5): 1 to 0	0			
Cycle 29 Day 1 (n=5): 1 to 2	0			
Cycle 29 Day 1 (n=5): 1 to 3	0			
Cycle 29 Day 1 (n=5): 1 to 4	0			
Cycle 30 Day 1 (n=3): Unchanged	66.7			
Cycle 30 Day 1 (n=3): 0 to 1	33.3			
Cycle 30 Day 1 (n=3): 0 to 2	0			
Cycle 30 Day 1 (n=3): 0 to 3	0			
Cycle 30 Day 1 (n=3): 0 to 4	0			
Cycle 30 Day 1 (n=3): 1 to 0	0			
Cycle 30 Day 1 (n=3): 1 to 2	0			
Cycle 30 Day 1 (n=3): 1 to 3	0			
Cycle 30 Day 1 (n=3): 1 to 4	0			
Cycle 31 Day 1 (n=1): Unchanged	100			
Cycle 31 Day 1 (n=1): 0 to 1	0			
Cycle 31 Day 1 (n=1): 0 to 2	0			
Cycle 31 Day 1 (n=1): 0 to 3	0			
Cycle 31 Day 1 (n=1): 0 to 4	0			
Cycle 31 Day 1 (n=1): 1 to 0	0			
Cycle 31 Day 1 (n=1): 1 to 2	0			
Cycle 31 Day 1 (n=1): 1 to 3	0			
Cycle 31 Day 1 (n=1): 1 to 4	0			
Cycle 32 Day 1 (n=1): Unchanged	0			
Cycle 32 Day 1 (n=1): 0 to 1	100			
Cycle 32 Day 1 (n=1): 0 to 2	0			
Cycle 32 Day 1 (n=1): 0 to 3	0			
Cycle 32 Day 1 (n=1): 0 to 4	0			
Cycle 32 Day 1 (n=1): 1 to 0	0			
Cycle 32 Day 1 (n=1): 1 to 2	0			
Cycle 32 Day 1 (n=1): 1 to 3	0			

Cycle 32 Day 1 (n=1): 1 to 4	0			
Cycle 33 Day 1 (n=1): Unchanged	100			
Cycle 33 Day 1 (n=1): 0 to 1	0			
Cycle 33 Day 1 (n=1): 0 to 2	0			
Cycle 33 Day 1 (n=1): 0 to 3	0			
Cycle 33 Day 1 (n=1): 0 to 4	0			
Cycle 33 Day 1 (n=1): 1 to 0	0			
Cycle 33 Day 1 (n=1): 1 to 2	0			
Cycle 33 Day 1 (n=1): 1 to 3	0			
Cycle 33 Day 1 (n=1): 1 to 4	0			
End of Treatment (n=1847): Unchanged	43.5			
End of Treatment (n=1847): 0 to 1	21.6			
End of Treatment (n=1847): 0 to 2	7			
End of Treatment (n=1847): 0 to 3	2.4			
End of Treatment (n=1847): 0 to 4	0.2			
End of Treatment (n=1847): 1 to 0	2.2			
End of Treatment (n=1847): 1 to 2	13.5			
End of Treatment (n=1847): 1 to 3	8.6			
End of Treatment (n=1847): 1 to 4	0.8			
End of Treatment (n=1847): Missing	0.3			

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 (± 3.9)			

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)	15.4 (± 16.4)			

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 (± 11.4)			

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 mg	31.1			
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%)	81 (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	NCI-CTCAE
Dictionary version	4.0

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). 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.

Serious adverse events	Regorafenib (BAY73-4506)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1251 / 2864 (43.68%)		
number of deaths (all causes)	405		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Tumor pain			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hematoma			

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphedema			
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		
Vascular disorders - Other			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Peripheral ischemia			
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		
Thromboembolic event			
subjects affected / exposed	23 / 2864 (0.80%)		
occurrences causally related to treatment / all	11 / 27		
deaths causally related to treatment / all	1 / 1		
Vasculitis			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical and medical procedures - Other			
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			
Death NOS			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	1 / 8		
Edema limbs			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	27 / 2864 (0.94%)		
occurrences causally related to treatment / all	21 / 30		
deaths causally related to treatment / all	0 / 0		
Flu like symptoms			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	72 / 2864 (2.51%)		
occurrences causally related to treatment / all	17 / 83		
deaths causally related to treatment / all	0 / 1		
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		

Localized edema			
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		
Multi-organ failure			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 4		
General disorders and administration site conditions - Other			
subjects affected / exposed	328 / 2864 (11.45%)		
occurrences causally related to treatment / all	23 / 497		
deaths causally related to treatment / all	3 / 238		
Non-cardiac chest pain			
subjects affected / exposed	13 / 2864 (0.45%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Sudden death NOS			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pain			
subjects affected / exposed	10 / 2864 (0.35%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders - Other			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine hemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
Vaginal fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vaginal hemorrhage			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Adult 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		
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		
Bronchopulmonary hemorrhage			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	3 / 7		
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		
Cough			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea			
subjects affected / exposed	37 / 2864 (1.29%)		
occurrences causally related to treatment / all	1 / 55		
deaths causally related to treatment / all	0 / 13		
Epistaxis			
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		
Hiccups			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	27 / 2864 (0.94%)		
occurrences causally related to treatment / all	0 / 38		
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		
Pneumonitis			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pneumothorax			
subjects affected / exposed	11 / 2864 (0.38%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 1		
Pulmonary edema			
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	17 / 2864 (0.59%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 15		
Voice alteration			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	13 / 2864 (0.45%)		
occurrences causally related to treatment / all	2 / 14		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
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		
Hallucinations			
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		
Psychosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 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	35 / 2864 (1.22%)		
occurrences causally related to treatment / all	13 / 51		
deaths causally related to treatment / all	0 / 1		
Cardiac troponin I increased			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GGT increased			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
INR increased			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	9 / 2864 (0.31%)		
occurrences causally related to treatment / all	20 / 21		
deaths causally related to treatment / all	0 / 0		
Investigations - Other			

subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT corrected interval prolonged				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Weight loss				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
White blood cell decreased				
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				
Burn				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
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			
Fracture				
subjects affected / exposed	8 / 2864 (0.28%)			
occurrences causally related to treatment / all	0 / 8			
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			
Intestinal stoma site bleeding				

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Intestinal stoma leak			
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 - Other			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal stoma obstruction			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Spinal fracture			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound complication			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
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		
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		
Acute coronary syndrome			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	3 / 8		
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		
Atrial flutter			
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	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	1 / 8		
Heart failure			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Chest pain - cardiac			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 3		
Cardiac disorders - Other			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pericarditis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
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		
Sinus bradycardia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 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		
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cognitive disturbance			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dysesthesia			
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	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Edema cerebral			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Intracranial hemorrhage			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	1 / 2		
Facial nerve disorder			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ischemia cerebrovascular			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Memory impairment			
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	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders - Other			
subjects affected / exposed	11 / 2864 (0.38%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 2		
Radiculitis			
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		
Seizure			
subjects affected / exposed	10 / 2864 (0.35%)		
occurrences causally related to treatment / all	0 / 11		
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			
Syncope				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Transient ischemic attacks				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	15 / 2864 (0.52%)			
occurrences causally related to treatment / all	8 / 23			
deaths causally related to treatment / all	0 / 0			
Hemolysis				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
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			
Blood and lymphatic system disorders - Other				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 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			
Corneal ulcer			
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		
Anal hemorrhage			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	65 / 2864 (2.27%)		
occurrences causally related to treatment / all	2 / 78		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	26 / 2864 (0.91%)		
occurrences causally related to treatment / all	0 / 34		
deaths causally related to treatment / all	0 / 5		
Colonic hemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Colonic fistula			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 1		
Colonic obstruction			
subjects affected / exposed	29 / 2864 (1.01%)		
occurrences causally related to treatment / all	0 / 37		
deaths causally related to treatment / all	0 / 4		
Colonic stenosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic perforation			
subjects affected / exposed	11 / 2864 (0.38%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	1 / 3		
Duodenal hemorrhage			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	13 / 2864 (0.45%)		
occurrences causally related to treatment / all	0 / 14		
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		
Diarrhea			
subjects affected / exposed	29 / 2864 (1.01%)		
occurrences causally related to treatment / all	26 / 34		
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		
Dyspepsia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Esophagitis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Esophageal hemorrhage			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Enterovesical fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Esophageal ulcer			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Esophageal varices hemorrhage			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
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		
Gastrointestinal fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric hemorrhage			
subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	1 / 2		
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		
Ileus			
subjects affected / exposed	14 / 2864 (0.49%)		
occurrences causally related to treatment / all	1 / 17		
deaths causally related to treatment / all	0 / 2		
Ileal fistula			

subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Ileal perforation			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal obstruction			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Ileal stenosis			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jejunal obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
Jejunal fistula			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal hemorrhage			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Mucositis oral			

subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	6 / 7		
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		
Oral pain			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstruction gastric			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders - Other			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	4 / 6		
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 fistula			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Rectal hemorrhage			

subjects affected / exposed	10 / 2864 (0.35%)			
occurrences causally related to treatment / all	2 / 12			
deaths causally related to treatment / all	0 / 1			
Rectal obstruction				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal hemorrhage				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
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			
Small intestinal perforation				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Small intestinal obstruction				
subjects affected / exposed	40 / 2864 (1.40%)			
occurrences causally related to treatment / all	2 / 51			
deaths causally related to treatment / all	0 / 6			
Upper gastrointestinal hemorrhage				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	2 / 5			
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			
Hepatobiliary disorders				
Bile duct stenosis				

subjects affected / exposed	31 / 2864 (1.08%)		
occurrences causally related to treatment / all	4 / 38		
deaths causally related to treatment / all	0 / 1		
Cholecystitis			
subjects affected / exposed	10 / 2864 (0.35%)		
occurrences causally related to treatment / all	1 / 15		
deaths causally related to treatment / all	0 / 1		
Gallbladder obstruction			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	35 / 2864 (1.22%)		
occurrences causally related to treatment / all	5 / 59		
deaths causally related to treatment / all	1 / 24		
Hepatic pain			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
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		
Hepatobiliary disorders - Other			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 1		
Portal 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		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders - Other			

subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash acneiform			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Palmar-plantar erythrodysesthesia 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 maculo-papular			
subjects affected / exposed	22 / 2864 (0.77%)		
occurrences causally related to treatment / all	28 / 29		
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		
Skin ulceration			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 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		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	27 / 2864 (0.94%)		
occurrences causally related to treatment / all	4 / 33		
deaths causally related to treatment / all	0 / 7		
Renal and urinary disorders - Other			

subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Cystitis noninfective				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal hemorrhage				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hematuria				
subjects affected / exposed	6 / 2864 (0.21%)			
occurrences causally related to treatment / all	0 / 6			
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 tract obstruction				
subjects affected / exposed	9 / 2864 (0.31%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Urinary tract pain				
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				
Hypothyroidism				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				

subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders - Other				
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				
Back pain				
subjects affected / exposed	30 / 2864 (1.05%)			
occurrences causally related to treatment / all	0 / 37			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	7 / 2864 (0.24%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Generalized muscle weakness				
subjects affected / exposed	4 / 2864 (0.14%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Chest wall pain				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
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			
Musculoskeletal and connective tissue disorder - Other				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pelvic soft tissue necrosis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle weakness lower limb				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle weakness right-sided				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anorectal infection				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Abdominal infection				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	15 / 2864 (0.52%)			
occurrences causally related to treatment / all	1 / 15			
deaths causally related to treatment / all	0 / 0			
Bronchial infection				

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter related infection			
subjects affected / exposed	8 / 2864 (0.28%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Esophageal infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Duodenal infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatic infection			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	54 / 2864 (1.89%)		
occurrences causally related to treatment / all	3 / 73		
deaths causally related to treatment / all	0 / 11		
Kidney infection			

subjects affected / exposed	5 / 2864 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infective myositis			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations - Other			
subjects affected / exposed	21 / 2864 (0.73%)		
occurrences causally related to treatment / all	2 / 22		
deaths causally related to treatment / all	0 / 1		
Papulopustular rash			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Peritoneal infection			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
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		
Pleural infection			
subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic infection			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
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			
Sepsis				
subjects affected / exposed	40 / 2864 (1.40%)			
occurrences causally related to treatment / all	6 / 52			
deaths causally related to treatment / all	2 / 13			
Skin infection				
subjects affected / exposed	2 / 2864 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Upper respiratory infection				
subjects affected / exposed	5 / 2864 (0.17%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	27 / 2864 (0.94%)			
occurrences causally related to treatment / all	0 / 29			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	3 / 2864 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 2864 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anorexia				

subjects affected / exposed	7 / 2864 (0.24%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Hypocalcemia			
subjects affected / exposed	1 / 2864 (0.03%)		
occurrences causally related to treatment / all	1 / 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		
Hypoglycemia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypokalemia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypophosphatemia			
subjects affected / exposed	3 / 2864 (0.10%)		
occurrences causally related to treatment / all	11 / 12		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	6 / 2864 (0.21%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Hyperkalemia			
subjects affected / exposed	4 / 2864 (0.14%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Hyperglycemia			

subjects affected / exposed	2 / 2864 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders - Other			
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	2785 / 2864 (97.24%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	995 / 2864 (34.74%)		
occurrences (all)	2549		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	153 / 2864 (5.34%)		
occurrences (all)	179		
Fever			
subjects affected / exposed	566 / 2864 (19.76%)		
occurrences (all)	761		
Fatigue			
subjects affected / exposed	1725 / 2864 (60.23%)		
occurrences (all)	3217		
General disorders and administration site conditions - Other			
subjects affected / exposed	167 / 2864 (5.83%)		
occurrences (all)	198		
Pain			
subjects affected / exposed	344 / 2864 (12.01%)		
occurrences (all)	508		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	226 / 2864 (7.89%)		
occurrences (all)	260		
Dyspnea			
subjects affected / exposed	370 / 2864 (12.92%)		
occurrences (all)	475		
Hoarseness			
subjects affected / exposed	424 / 2864 (14.80%)		
occurrences (all)	508		
Voice alteration			
subjects affected / exposed	373 / 2864 (13.02%)		
occurrences (all)	482		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	149 / 2864 (5.20%)		
occurrences (all)	163		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	269 / 2864 (9.39%)		
occurrences (all)	497		
Alkaline phosphatase increased			
subjects affected / exposed	189 / 2864 (6.60%)		
occurrences (all)	255		
Aspartate aminotransferase increased			
subjects affected / exposed	330 / 2864 (11.52%)		
occurrences (all)	567		
Lipase increased			
subjects affected / exposed	242 / 2864 (8.45%)		
occurrences (all)	525		
Blood bilirubin increased			
subjects affected / exposed	604 / 2864 (21.09%)		
occurrences (all)	1306		
Weight loss			

subjects affected / exposed	872 / 2864 (30.45%)		
occurrences (all)	1135		
Platelet count decreased			
subjects affected / exposed	225 / 2864 (7.86%)		
occurrences (all)	339		
Nervous system disorders			
Headache			
subjects affected / exposed	296 / 2864 (10.34%)		
occurrences (all)	375		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	308 / 2864 (10.75%)		
occurrences (all)	586		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	561 / 2864 (19.59%)		
occurrences (all)	777		
Diarrhea			
subjects affected / exposed	912 / 2864 (31.84%)		
occurrences (all)	1804		
Constipation			
subjects affected / exposed	497 / 2864 (17.35%)		
occurrences (all)	600		
Nausea			
subjects affected / exposed	483 / 2864 (16.86%)		
occurrences (all)	635		
Dry mouth			
subjects affected / exposed	151 / 2864 (5.27%)		
occurrences (all)	173		
Mucositis oral			
subjects affected / exposed	780 / 2864 (27.23%)		
occurrences (all)	1164		
Vomiting			

subjects affected / exposed	375 / 2864 (13.09%)		
occurrences (all)	516		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1220 / 2864 (42.60%)		
occurrences (all)	3167		
Rash maculo-papular			
subjects affected / exposed	310 / 2864 (10.82%)		
occurrences (all)	445		
Dry skin			
subjects affected / exposed	178 / 2864 (6.22%)		
occurrences (all)	241		
Rash acneiform			
subjects affected / exposed	180 / 2864 (6.28%)		
occurrences (all)	252		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	268 / 2864 (9.36%)		
occurrences (all)	443		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	177 / 2864 (6.18%)		
occurrences (all)	212		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	181 / 2864 (6.32%)		
occurrences (all)	225		
Pain in extremity			
subjects affected / exposed	191 / 2864 (6.67%)		
occurrences (all)	259		
Back pain			
subjects affected / exposed	273 / 2864 (9.53%)		
occurrences (all)	376		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	211 / 2864 (7.37%) 255		
Metabolism and nutrition disorders Hypophosphatemia subjects affected / exposed occurrences (all)	333 / 2864 (11.63%) 786		
Anorexia subjects affected / exposed occurrences (all)	997 / 2864 (34.81%) 1407		
Hypokalemia subjects affected / exposed occurrences (all)	197 / 2864 (6.88%) 290		

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