Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Phase III Study of Regorafenib Plus BSC Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer (CRC) Who Have Progressed After Standard Therapy

Summary

EudraCT number	2009-012787-14
Trial protocol	BE DE HU PT ES CZ IT FR NL
Global end of trial date	22 January 2014

Results information

Result version number	v2 (current)
This version publication date	03 September 2016
First version publication date	12 June 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/14387

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01103323
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of regorafenib in subjects with metastatic CRC who have progressed after standard therapies.

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. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only subjects who voluntarily signed the informed consent form, were able to enter the study.

Background therapy:

Best supportive care (BSC) includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

Evidence for comparator: -

Actual start date of recruitment	30 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Spain: 83
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 87
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	France: 116
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Israel: 14

Country: Number of subjects enrolled	Italy: 143
Worldwide total number of subjects	760
EEA total number of subjects	526

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)	475
From 65 to 84 years	284
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This multinational study was conducted at 114 centers that enrolled subjects across 16 countries.

Pre-assignment

Screening details:

Of the 1052 subjects who completed screening, 760 subjects were randomized and 292 subjects who signed the informed consent but were never randomized, were considered as screening failures.

Period 1

Period 1 title	Without/Before Drug Switch
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

For subjects without drug switch (subjects on regorafenib or subjects on placebo without cross-over to regorafenib), the period 1 included both double-blinded and open label. Period 1 was not double-blinded only for these subjects.
Only for 4 subjects on placebo who were crossed-over to regorafenib, period 1 was before cross-over (placebo period) and period 2 was after cross-over (regorafenib period).

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib (Stivarga, BAY73-4506) + BSC

Arm description:

Subjects received regorafenib 160 milligram (mg) per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

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

Dosage and administration details:

Subjects received regorafenib 160 mg per oral once daily for 3 weeks on 1 week off of every 4 week cycle.

Arm title	Placebo + BSC

Arm description:

Subjects received matching placebo tablets per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

Arm type	Placebo

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

Dosage and administration details:

Subjects received matching placebo tablets per oral once daily for 3 weeks on 1 week off of every 4 week cycle.

Number of subjects in period 1	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC
Started	505	255
Treated	500	253
Completed	429	237
Not completed	76	18
Physician decision	2	-
Consent withdrawn by subject	17	5
Adverse event	50	7
Protocol Violation	2	-
Switch to Regorafenib	-	4
Did not receive study treatment	5	2

Period 2

Period 2 title	Switched From Placebo to Regorafenib
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Placebo - Regorafenib After Unblinding

Arm description:

Subjects in the placebo + BSC group switched to treatment with regorafenib after unblinding. It is for regorafenib treatment period only.

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

Dosage and administration details:

Subjects received regorafenib 160 mg per oral once daily for 3 weeks on 1 week off of every 4 week cycle.

Number of subjects in period 2[1]	Placebo - Regorafenib After Unblinding
Started	4
Completed	3
Not completed	1
Adverse event	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 1 placebo arm was placebo and placebo-regorafenib with placebo period only. Period 2 was placebo-regorafenib with regorafenib period only. Not every subject in placebo arm was crossed-over to regorafenib treatment in Period 2. In reality, 4 subjects in the placebo group switched to regorafenib treatment after unblinding. Only few placebo subjects were on treatment when the positive study outcome became available and cross-over was possible.

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib (Stivarga, BAY73-4506) + BSC
Reporting group description:	
Subjects received regorafenib 160 milligram (mg) per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.	
Reporting group title	Placebo + BSC
Reporting group description:	
Subjects received matching placebo tablets per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.	

Reporting group values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC	Total
Number of subjects	505	255	760
Age categorical			
Units: Subjects			
Age continuous			
The age of the subject in years at enrolment in the study.			
Units: years			
arithmetic mean	60.7	60.1	
full range (min-max)	22 to 82	25 to 85	-
Gender categorical			
Units: Subjects			
Male	311	153	464
Female	194	102	296
Eastern Cooperative Oncology Group (ECOG) performance status (PS) before treatment			
ECOG PS is a scale that measures how cancer affects the daily life of a subject on an ordinal scale from grade 0 (best) to grade 5 (worst). 0=Fully active without restriction; 1= Restricted in physically strenuous activity; 2= Ambulatory, capable of all selfcare; 3= Capable of limited selfcare; 4= Completely disabled; 5= Dead.			
Units: Subjects			
grade 0	265	146	411
grade 1	240	109	349
KRAS mutation			
Kirsten rat sarcoma viral oncogene homolog (protein), member of the RAS family of GTPases (guanosine triphosphate hydrolases).			
Units: Subjects			
No	205	94	299
Yes	273	157	430
Unknown	27	4	31

End points

End points reporting groups

Reporting group title	Regorafenib (Stivarga, BAY73-4506) + BSC

Reporting group description:

Subjects received regorafenib 160 milligram (mg) per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

Reporting group title	Placebo + BSC

Reporting group description:

Subjects received matching placebo tablets per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

Reporting group title	Placebo - Regorafenib After Unblinding

Reporting group description:

Subjects in the placebo + BSC group switched to treatment with regorafenib after unblinding. It is for regorafenib treatment period only.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time (days) from randomization to death due to any cause. Subjects alive at the time of analysis were censored at the last date known to be alive. If a subject was lost to follow-up and there was no contact after randomization, this subject was censored at Day 1. Efficacy data were of double-blind period and up to 21 July 2011.

End point type	Primary

End point timeframe:

From randomization of the first subject until the database cut-off approximately 14 months later (19May2010 - 21Jul2011) used for 2nd planned formal interim analysis (IA)

End point values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505[1]	255[2]		
Units: Days				
median (confidence interval 95%)	196 (178 to 222)	151 (134 to 177)		

Notes:

[1] - Intention-to-treat (ITT) population included all randomized subjects.

[2] - ITT population included all randomized subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis for Overall Survival

Statistical analysis description:

Sample size based on primary efficacy endpoint of OS. The study was designed to have 90% power to detect 33.3% increase in median OS (i.e. hazard ratio of 0.75, regorafenib / placebo). Assuming 1-sided overall alpha of 0.025, randomization ratio of 2:1 for regorafenib and placebo, and 2 formal interim analyses of OS using an O'Brien-Fleming-type error spending function, a total of 582 death events were required for primary completion. Results based on 2nd planned formal IA with 432 total events.

Comparison groups	Regorafenib (Stivarga, BAY73-4506) + BSC v Placebo + BSC
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.005178 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	0.942

Notes:

[3] - Two treatment groups compared using a stratified log-rank test, randomization was stratified by prior treatment with vascular endothelial growth factor-targeting drugs, time from diagnosis of metastatic disease, and geographical region. Hazard ratio (regorafenib / placebo) and its 95% confidence interval calculated using Cox model, stratified by same factors.
[4] - According to protocol specified O'Brien-Fleming type alpha spending function and 432 death events at 2nd IA, the pre-specified alpha (false positive rate) for this analysis was 0.009279 (1-sided).

Secondary: Progression-free Survival (Based on Investigator's Assessment)

End point title	Progression-free Survival (Based on Investigator's Assessment)

End point description:

Progression-free survival was defined as the time (days) from date of randomization to date of first observed disease progression (radiological or clinical) or death due to any cause, if death occurred before progression was documented.
Efficacy data were of double-blind period and up to 21 July 2011.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off approximately 14 months later (19May2010 - 21Jul2011) used for 2nd planned formal IA. Tumor assessed at 8 week intervals.

End point values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505[5]	255[6]		
Units: Days				
median (confidence interval 95%)	59 (57 to 65)	52 (51 to 53)		

Notes:

[5] - ITT population included all randomized subjects.

[6] - ITT population included all randomized subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis for Progression-free Survival

Statistical analysis description:

Two treatment groups compared using a stratified log-rank test, stratified by same stratification factors as randomization. Hazard ratio (regorafenib / placebo) and its 95% confidence interval calculated using Cox model, stratified by same factors.

Comparison groups	Regorafenib (Stivarga, BAY73-4506) + BSC v Placebo + BSC
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.494
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.419
upper limit	0.582

Notes:

[7] - Comparison based on pre-specified alpha level of 0.025 (1-sided).

Secondary: Objective Tumor Response

End point title	Objective Tumor Response

End point description:

The objective tumor response was defined as the percentage of subjects with complete response (CR, tumor disappears) or partial response (PR, sum of lesion sizes decreased at least 30% from baseline) as best overall response. A best overall response was defined for all subjects, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1. Subjects whose best overall response was not CR or PR, and any subjects with no post-baseline assessments were considered non-responders for the analysis.
Efficacy data were of double-blind period and up to 21 July 2011.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off approximately 14 months later (19May2010 - 21Jul2011) used for 2nd planned formal IA. Tumor assessed at 8 week intervals.

End point values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505[8]	255[9]		
Units: Percentage of subjects				
number (not applicable)	1	0.4		

Notes:

[8] - ITT population included all randomized subjects.

[9] - ITT population included all randomized subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis for Objective Tumor Response

Statistical analysis description:

Two treatment groups compared using Cochran-Mantel-Haenszel (CMH) test adjusting for same stratification factors as at randomization.
The below parameter estimate 'difference' = Placebo - Regorafenib 160 mg.

Comparison groups	Regorafenib (Stivarga, BAY73-4506) + BSC v Placebo + BSC
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188432 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	0.53

Notes:

[10] - Comparison based on pre-specified alpha level of 0.025 (1-sided).

Secondary: Disease Control

End point title	Disease Control

End point description:

Disease control was defined as the percentage of subjects whose best response was not PD [sum of lesion sizes increased at least 20% from smallest sum on study or new lesions] (that was, CR [tumor disappeared], PR [sum of lesion sizes decreased at least 30% from baseline] or SD (stable disease)). SD included if at least 6 weeks after randomization.
Efficacy data were of double-blind period and up to 21 July 2011.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off approximately 14 months later (19May2010 - 21Jul2011) used for 2nd planned formal IA. Tumor assessed at 8 week intervals.

End point values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505[11]	255[12]		
Units: Percentage of subjects				
number (not applicable)	41	14.9		

Notes:

[11] - ITT population included all randomized subjects.

[12] - ITT population included all randomized subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis for Disease Control

Statistical analysis description:

Two treatment groups compared using CMH test adjusting for same stratification factors as at

randomization.
The below parameter estimate 'difference' = Placebo - Regorafenib 160 mg.

Comparison groups	Regorafenib (Stivarga, BAY73-4506) + BSC v Placebo + BSC
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-25.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.06
upper limit	-19.82

Notes:

[13] - Comparison based on pre-specified alpha level of 0.025 (1-sided).

Secondary: Tumor Response

End point title	Tumor Response

End point description:

A tumor response (best overall response) was defined for all subjects, using the RECIST criteria, version 1.1.
Categories: complete response (CR, tumor disappears), partial response (PR, sum of lesion sizes decreased at least 30% from baseline), stable disease (SD, steady state of disease which was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease [PD], no unequivocal progression of existing non target lesions and no appearance of new lesions), PD (sum of lesion sizes increased at least 20% from smallest sum on study or new lesions), non CR/non PD. Clinical PD considered when radiographic imaging not possible.
Efficacy data were of double-blind period and up to 21 July 2011.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off approximately 14 months later (19May2010 - 21Jul2011) used for 2nd planned formal IA. Tumor assessed at 8 week intervals.

End point values	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505[14]	255[15]		
Units: Percentage of subjects				
number (not applicable)				
Complete Response (CR)	0	0		
Partial Response (PR)	1	0.4		
Stable Disease (SD)	42.8	14.5		
Progressive Disease (PD)	49.5	80		
Non CR/Non PD	0.8	0.4		
Not applicable	0.2	0		
Not assessed	5.7	4.7		

Notes:

[14] - ITT population included all randomized subjects.

[15] - ITT population included all randomized subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected up to 30 days after end of study treatment (per protocol) over a period of approximately 3.7 years (19 May 2010 [first subject randomized] to 22 January 2014 [last subject last visit])

Adverse event reporting additional description:

All subjects who were randomized and received at least 1 dose of study drug were included in the safety analyses.

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Regorafenib (Stivarga, BAY73-4506) + BSC

Reporting group description:

Subjects received regorafenib 160 mg per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy.

Reporting group title	Placebo - Regorafenib after unblinding

Reporting group description:

Participants in the placebo + BSC group crossed over to treatment with Regorafenib after unblinding. It is for Regorafenib treatment period only

Reporting group title	Placebo + BSC

Reporting group description:

Subjects received matching placebo tablets per oral once daily for 3 weeks on 1 week off of every 4 week cycle plus BSC. BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immuno-therapy. This group included subjects on placebo without cross-over to regorafenib and subjects on placebo who were crossed-over to regorafenib with placebo period only.

Serious adverse events	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo - Regorafenib after unblinding	Placebo + BSC
Total subjects affected by serious adverse events			
subjects affected / exposed	232 / 500 (46.40%)	2 / 4 (50.00%)	103 / 253 (40.71%)
number of deaths (all causes)	476	2	235
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy (possibly related to cancer treatment)			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hemorrhage pulmonary, Bronchus			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hemorrhage pulmonary, Mediastinum			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Abdomen NOS			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hemorrhage, GI, Anus			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hemorrhage, GI, Lower GI NOS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Rectum			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Stoma			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Upper GI NOS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Varices (esophageal)			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Varices (rectal)			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GU, Vagina			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thrombosis/Embolism (vascular access)			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis/Thrombus/Embolism			
subjects affected / exposed	6 / 500 (1.20%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	1 / 6	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular - Other			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Constitutional symptoms - Other			
subjects affected / exposed	34 / 500 (6.80%)	0 / 4 (0.00%)	23 / 253 (9.09%)
occurrences causally related to treatment / all	1 / 49	0 / 0	0 / 39
deaths causally related to treatment / all	0 / 23	0 / 0	0 / 18
Death not associated with CTCAE term, Disease progression NOS			
subjects affected / exposed	16 / 500 (3.20%)	1 / 4 (25.00%)	6 / 253 (2.37%)
occurrences causally related to treatment / all	0 / 17	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 16	0 / 1	0 / 6
Death not associated with CTCAE term, Multi-Organ Failure			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 1
Death not associated with CTCAE term, Sudden death			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 2
Fatigue			
subjects affected / exposed	5 / 500 (1.00%)	0 / 4 (0.00%)	5 / 253 (1.98%)
occurrences causally related to treatment / all	3 / 6	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	17 / 500 (3.40%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	8 / 21	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pain, Abdomen NOS			
subjects affected / exposed	13 / 500 (2.60%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 21	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain, Back			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	4 / 253 (1.58%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Buttock			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Cardiac/Heart			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Chest wall			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Chest/Thorax NOS			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Extremity - limb			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Head/Headache			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Joint			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Liver			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Neuralgia/Peripheral nerve			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Pain NOS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Tumor pain			
subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syndromes - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumor flare			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight loss			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

ARDS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cough			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea (Shortness of breath)			
subjects affected / exposed	12 / 500 (2.40%)	0 / 4 (0.00%)	4 / 253 (1.58%)
occurrences causally related to treatment / all	1 / 18	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 6	0 / 0	0 / 2
Pleural effusion			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	4 / 253 (1.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrhythmia - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ischemia/infarction			

subjects affected / exposed	6 / 500 (1.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hypertension			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Supraventricular arrhythmia, Atrial fibrillation			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cTnT			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CNS ischemia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cognitive disturbance			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mood Alteration, Anxiety			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurology - Other			
subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neuropathy: Cranial, CN III Pupil, upper eyelid, extra ocular mov			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy: motor			
subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech impairment			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope (Fainting)			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
DIC			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema: Limb			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema: Trunk/Genital			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema: Viscera			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemoglobin			

subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	3 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INR			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophils			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelets			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ocular - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	5 / 500 (1.00%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	7 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			

subjects affected / exposed	1 / 500 (0.20%)	1 / 4 (25.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea			
subjects affected / exposed	8 / 500 (1.60%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	8 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distension			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula, GI, Abdomen NOS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula, GI, Anus			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula, GI, Small bowel NOS			

subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GI - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hemorrhoids			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Mucositis (functional/symptomatic), Small bowel			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrosis, GI, Peritoneal cavity			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GI, Colon			
subjects affected / exposed	9 / 500 (1.80%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Obstruction, GI, Ileum			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GI, Small bowel NOS			

subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	7 / 253 (2.77%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Obstruction, GI, Stomach			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforation, GI, Colon			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stricture, GI, Biliary tree			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer, GI, Duodenum			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 500 (0.60%)	1 / 4 (25.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary - Other			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver dysfunction			

subjects affected / exposed	17 / 500 (3.40%)	0 / 4 (0.00%)	5 / 253 (1.98%)
occurrences causally related to treatment / all	6 / 28	0 / 0	0 / 11
deaths causally related to treatment / all	2 / 11	0 / 0	0 / 5
Skin and subcutaneous tissue disorders			
Dermatology - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Erythema multiforme			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand-foot skin reaction			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash/Desquamation			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication, non-infectious			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula, GU, Bladder			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GU, Ureter			

subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal - Other			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	5 / 500 (1.00%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	2 / 6	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Urinary retention			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait/Walking			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness left-sided			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness, Extremity - lower			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness, Whole body/generalized			

subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection (documented clinically), Abdomen NOS			
subjects affected / exposed	4 / 500 (0.80%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Anal/perianal			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Appendix			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Bladder (urinary)			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Blood			

subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	2 / 253 (0.79%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Bronchus			
subjects affected / exposed	3 / 500 (0.60%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Catheter-related			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Kidney			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Lung (Pneumonia)			
subjects affected / exposed	9 / 500 (1.80%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 2
Infection (documented clinically), Skin (Cellulitis)			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Soft tissue NOS			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Urinary tract NOS			

subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically), Wound			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection - Other			
subjects affected / exposed	5 / 500 (1.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infection with normal ANC, Blood			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Catheter-related			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Colon			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Gallbladder (Cholecystitis)			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Kidney			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Lung			

(Pneumonia)			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Soft tissue NOS			
subjects affected / exposed	2 / 500 (0.40%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Kidney			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Lung (Pneumonia)			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
AST			
subjects affected / exposed	0 / 500 (0.00%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin (Hyperbilirubinemia)			
subjects affected / exposed	8 / 500 (1.60%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences causally related to treatment / all	2 / 11	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminemia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcemia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyponatremia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic/Lab - Other			
subjects affected / exposed	1 / 500 (0.20%)	0 / 4 (0.00%)	0 / 253 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Regorafenib (Stivarga, BAY73-4506) + BSC	Placebo - Regorafenib after unblinding	Placebo + BSC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	489 / 500 (97.80%)	4 / 4 (100.00%)	229 / 253 (90.51%)
Vascular disorders			
Hemorrhage pulmonary, Nose			
subjects affected / exposed	45 / 500 (9.00%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences (all)	55	0	6
Cardiac disorders			
Hypertension			
subjects affected / exposed	155 / 500 (31.00%)	1 / 4 (25.00%)	21 / 253 (8.30%)
occurrences (all)	213	1	23
Nervous system disorders			
Neuropathy: sensory			
subjects affected / exposed	51 / 500 (10.20%)	0 / 4 (0.00%)	25 / 253 (9.88%)
occurrences (all)	68	0	27
Dizziness			
subjects affected / exposed	28 / 500 (5.60%)	0 / 4 (0.00%)	13 / 253 (5.14%)
occurrences (all)	31	0	13
Blood and lymphatic system disorders			
Edema: Limb			
subjects affected / exposed	49 / 500 (9.80%)	0 / 4 (0.00%)	16 / 253 (6.32%)
occurrences (all)	57	0	19
Hemoglobin			
subjects affected / exposed	76 / 500 (15.20%)	0 / 4 (0.00%)	29 / 253 (11.46%)
occurrences (all)	142	0	46

Platelets			
subjects affected / exposed	79 / 500 (15.80%)	1 / 4 (25.00%)	6 / 253 (2.37%)
occurrences (all)	136	2	9
General disorders and administration site conditions			
Constitutional symptoms - Other			
subjects affected / exposed	30 / 500 (6.00%)	0 / 4 (0.00%)	17 / 253 (6.72%)
occurrences (all)	33	0	19
Fatigue			
subjects affected / exposed	318 / 500 (63.60%)	0 / 4 (0.00%)	115 / 253 (45.45%)
occurrences (all)	612	0	168
Fever			
subjects affected / exposed	136 / 500 (27.20%)	2 / 4 (50.00%)	40 / 253 (15.81%)
occurrences (all)	189	3	48
Flu-like syndrome			
subjects affected / exposed	27 / 500 (5.40%)	1 / 4 (25.00%)	6 / 253 (2.37%)
occurrences (all)	30	1	8
Insomnia			
subjects affected / exposed	39 / 500 (7.80%)	0 / 4 (0.00%)	14 / 253 (5.53%)
occurrences (all)	43	0	15
Pain, Abdomen NOS			
subjects affected / exposed	121 / 500 (24.20%)	0 / 4 (0.00%)	47 / 253 (18.58%)
occurrences (all)	239	0	53
Pain, Back			
subjects affected / exposed	79 / 500 (15.80%)	0 / 4 (0.00%)	25 / 253 (9.88%)
occurrences (all)	114	0	27
Pain, Buttock			
subjects affected / exposed	4 / 500 (0.80%)	1 / 4 (25.00%)	0 / 253 (0.00%)
occurrences (all)	5	1	0
Pain, Chest/Thorax NOS			
subjects affected / exposed	26 / 500 (5.20%)	0 / 4 (0.00%)	12 / 253 (4.74%)
occurrences (all)	29	0	14
Pain, Extremity - limb			
subjects affected / exposed	51 / 500 (10.20%)	0 / 4 (0.00%)	14 / 253 (5.53%)
occurrences (all)	83	0	19
Pain, Head/Headache			

subjects affected / exposed	50 / 500 (10.00%)	0 / 4 (0.00%)	18 / 253 (7.11%)
occurrences (all)	65	0	23
Pain, Joint			
subjects affected / exposed	32 / 500 (6.40%)	0 / 4 (0.00%)	13 / 253 (5.14%)
occurrences (all)	34	0	14
Pain, Muscle			
subjects affected / exposed	50 / 500 (10.00%)	0 / 4 (0.00%)	14 / 253 (5.53%)
occurrences (all)	64	0	16
Pain, Throat/Pharynx/Larynx			
subjects affected / exposed	9 / 500 (1.80%)	1 / 4 (25.00%)	1 / 253 (0.40%)
occurrences (all)	12	1	1
Weight loss			
subjects affected / exposed	167 / 500 (33.40%)	2 / 4 (50.00%)	30 / 253 (11.86%)
occurrences (all)	240	7	34
Eye disorders			
Ocular - Other			
subjects affected / exposed	5 / 500 (1.00%)	1 / 4 (25.00%)	0 / 253 (0.00%)
occurrences (all)	5	1	0
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	239 / 500 (47.80%)	0 / 4 (0.00%)	73 / 253 (28.85%)
occurrences (all)	388	0	96
Ascites			
subjects affected / exposed	23 / 500 (4.60%)	1 / 4 (25.00%)	6 / 253 (2.37%)
occurrences (all)	24	1	8
Constipation			
subjects affected / exposed	119 / 500 (23.80%)	0 / 4 (0.00%)	48 / 253 (18.97%)
occurrences (all)	147	0	58
Diarrhea			
subjects affected / exposed	218 / 500 (43.60%)	2 / 4 (50.00%)	44 / 253 (17.39%)
occurrences (all)	514	2	57
Fistula, GI, Colon/Cecum/Appendix			
subjects affected / exposed	0 / 500 (0.00%)	1 / 4 (25.00%)	0 / 253 (0.00%)
occurrences (all)	0	1	0
Mucositis (functional/symptomatic), Oral cavity			

subjects affected / exposed	145 / 500 (29.00%)	0 / 4 (0.00%)	12 / 253 (4.74%)
occurrences (all)	267	0	12
Nausea			
subjects affected / exposed	115 / 500 (23.00%)	1 / 4 (25.00%)	55 / 253 (21.74%)
occurrences (all)	162	1	67
Taste alteration			
subjects affected / exposed	39 / 500 (7.80%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences (all)	44	0	6
Vomiting			
subjects affected / exposed	85 / 500 (17.00%)	1 / 4 (25.00%)	41 / 253 (16.21%)
occurrences (all)	144	3	50
Hepatobiliary disorders			
Hepatobiliary - Other			
subjects affected / exposed	8 / 500 (1.60%)	1 / 4 (25.00%)	4 / 253 (1.58%)
occurrences (all)	9	3	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	56 / 500 (11.20%)	1 / 4 (25.00%)	28 / 253 (11.07%)
occurrences (all)	77	1	32
Dyspnea (Shortness of breath)			
subjects affected / exposed	89 / 500 (17.80%)	0 / 4 (0.00%)	34 / 253 (13.44%)
occurrences (all)	110	0	46
Voice changes			
subjects affected / exposed	160 / 500 (32.00%)	1 / 4 (25.00%)	16 / 253 (6.32%)
occurrences (all)	211	1	17
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	39 / 500 (7.80%)	0 / 4 (0.00%)	4 / 253 (1.58%)
occurrences (all)	43	0	4
Cheilitis			
subjects affected / exposed	4 / 500 (0.80%)	1 / 4 (25.00%)	0 / 253 (0.00%)
occurrences (all)	4	3	0
Dermatology - Other			
subjects affected / exposed	30 / 500 (6.00%)	0 / 4 (0.00%)	7 / 253 (2.77%)
occurrences (all)	45	0	10
Dry skin			

subjects affected / exposed	50 / 500 (10.00%)	0 / 4 (0.00%)	10 / 253 (3.95%)
occurrences (all)	59	0	11
Hand-foot skin reaction			
subjects affected / exposed	235 / 500 (47.00%)	1 / 4 (25.00%)	19 / 253 (7.51%)
occurrences (all)	720	3	21
Pruritus			
subjects affected / exposed	29 / 500 (5.80%)	0 / 4 (0.00%)	11 / 253 (4.35%)
occurrences (all)	39	0	11
Rash/Desquamation			
subjects affected / exposed	145 / 500 (29.00%)	1 / 4 (25.00%)	13 / 253 (5.14%)
occurrences (all)	211	2	17
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	27 / 500 (5.40%)	1 / 4 (25.00%)	1 / 253 (0.40%)
occurrences (all)	29	1	1
Metabolism and nutrition disorders			
ALT			
subjects affected / exposed	28 / 500 (5.60%)	0 / 4 (0.00%)	7 / 253 (2.77%)
occurrences (all)	53	0	8
AST			
subjects affected / exposed	37 / 500 (7.40%)	0 / 4 (0.00%)	12 / 253 (4.74%)
occurrences (all)	72	0	13
Alkaline phosphatase			
subjects affected / exposed	35 / 500 (7.00%)	0 / 4 (0.00%)	8 / 253 (3.16%)
occurrences (all)	49	0	12
Bilirubin (Hyperbilirubinemia)			
subjects affected / exposed	97 / 500 (19.40%)	1 / 4 (25.00%)	22 / 253 (8.70%)
occurrences (all)	160	3	37
Creatinine			
subjects affected / exposed	15 / 500 (3.00%)	1 / 4 (25.00%)	7 / 253 (2.77%)
occurrences (all)	19	2	8
GFR			
subjects affected / exposed	4 / 500 (0.80%)	1 / 4 (25.00%)	1 / 253 (0.40%)
occurrences (all)	9	1	2
Hypocalcemia			

subjects affected / exposed	34 / 500 (6.80%)	0 / 4 (0.00%)	1 / 253 (0.40%)
occurrences (all)	57	0	1
Hyperuricemia			
subjects affected / exposed	12 / 500 (2.40%)	1 / 4 (25.00%)	1 / 253 (0.40%)
occurrences (all)	13	1	1
Hypokalemia			
subjects affected / exposed	50 / 500 (10.00%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences (all)	84	0	7
Hyponatremia			
subjects affected / exposed	32 / 500 (6.40%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences (all)	43	0	10
Hypophosphatemia			
subjects affected / exposed	32 / 500 (6.40%)	1 / 4 (25.00%)	2 / 253 (0.79%)
occurrences (all)	62	2	3
Lipase			
subjects affected / exposed	32 / 500 (6.40%)	0 / 4 (0.00%)	3 / 253 (1.19%)
occurrences (all)	74	0	4
Metabolic/Lab - Other			
subjects affected / exposed	42 / 500 (8.40%)	0 / 4 (0.00%)	8 / 253 (3.16%)
occurrences (all)	69	0	15
Proteinuria			
subjects affected / exposed	40 / 500 (8.00%)	0 / 4 (0.00%)	6 / 253 (2.37%)
occurrences (all)	109	0	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2010	1. Clarifications were provided for: a. Inclusion criteria b. Exclusion criteria c. Re-screening of screen failures d. Guidance on missed or vomited tablets e. Dose modification/delay f. Permitted concomitant medications g. Non-permissible concomitant medications and procedures i. Pharmacokinetic sampling h. Study procedures/assessments 2. Synopsis was updated with changes to the inclusion/exclusion criteria 3. Updates to adverse events of special safety interest 4. Methods of measurement in RECIST (appendix) was updated 5. Examples of substrates of human liver microsomal P450 enzymes and examples of excluded traditional Chinese medicine were added 6. Approved standard therapies in anticipated participating countries was updated with new country information
03 August 2011	1. To exclude liver function test abnormalities 2. Dose modifications for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin increases related to study treatment 3. Guidance regarding subjects with diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake was added 4. Text was added to Treatment compliance section regarding use of subject drug diary 5. Schedule of Assessments was updated to include weekly checks of ALT, AST and bilirubin during the first two cycles of treatment 6. Adverse events of special safety interest was updated to add clarification regarding reporting of the adverse events of special interest
01 November 2011	'Treatments to be administered' section was updated to allow subjects on placebo treatment to receive regorafenib through open label treatment after positive outcome of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

At 2nd IA, pre-specified O'Brien-Fleming-type efficacy boundary was crossed. DMC concluded OS result positive and after positive risk benefit assessment, recommended unblinding of study. OS from 2nd IA were the final formal and definitive results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22421192

http://www.ncbi.nlm.nih.gov/pubmed/23177514