Clinical trial results:
A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer

Summary

EudraCT number	2009-012007-25
Trial protocol	DE GB ES IT NL FR DK SE BE AT SK BG
Global end of trial date	30 August 2017

Results information

Result version number	v2 (current)
This version publication date	17 February 2019
First version publication date	30 August 2018
Version creation reason	• Correction of full data set Control of data.

Trial information

Trial identification

Sponsor protocol code	14295

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00984282
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this phase III study in subjects with differentiated thyroid cancer (papillary, follicular, Hurthle cell carcinoma) who are refractory to radioactive iodine treatment is to compare the treatment groups in terms of progression free survival (PFS) evaluated by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.

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	15 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	United States: 97
Country: Number of subjects enrolled	China: 56
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Saudi Arabia: 6
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 5

Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 83
Worldwide total number of subjects	556
EEA total number of subjects	334

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)	310
From 65 to 84 years	242
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 81 study centers in Austria, Belgium, Bulgaria, China, Germany, Denmark, Spain, France, United Kingdom, Italy, Japan, Republic of Korea, Netherlands, Poland, Russia, Saudi-Arabia, Sweden and United States between 15 Oct 2009 (first subject first visit) and 30 Aug 2017 (last subject last visit)

Pre-assignment

Screening details:

A total of 556 subjects were screened. 137 subjects failed screening. 419 subjects were randomized but 2 subjects who did not meet the eligibility criteria were erroneously randomized to sorafenib, these subjects were never treated and were subsequently rescreened and randomized to placebo. 417 subjects were assigned to treatment.

Period 1

Period 1 title	Double blind treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib (Nexavar, BAY43-9006)

Arm description:

Participants received 2 tablets of Sorafenib (2×200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 400 mg will be administered orally, twice daily (approximately every 12 hours).

Arm title	Placebo

Arm description:

Participants received 2 tablets of Sorafenib-matching placebo orally twice daily (12 hours apart without food), 28 days comprise a cycle

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:

Placebo (2 tablets) will be administered orally, twice daily (approximately every 12 hours).

Number of subjects in period 1[1]	Sorafenib (Nexavar, BAY43-9006)	Placebo
Started	207	210
Completed	103	172
Not completed	104	38
Physician decision	1	2
Transferred to treatment continuation study	2	1
Adverse Event	40	6
Protocol driven decision point	1	1
Progression, recurrence or relapse	25	3
Radiological and clinical progression	-	1
Not treated	-	1
Consent withdrawn by subject	13	18
Switched to commercial drug	6	1
Death	8	4
Noncompliance with study medication	3	-
Lost to follow-up	3	-
Progression by clinical judgment	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all subjects completing double blinded treatment received Open-label treatment.

Period 2

Period 2 title	Open-label treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DB sorafenib first, then option of OL sorafenib treatment

Arm description:

Participants received 2 tablets of Sorafenib (2×200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 400 mg will be administered orally, twice daily (approximately every 12 hours).

Arm title	DB placebo first, then option of OL sorafenib treatment

Arm description:

Participants on placebo who switched to sorafenib, received sorafenib 400 mg (2 x 200 mg) orally twice daily, 28 days comprise a cycle.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 400 mg will be administered orally, twice daily (approximately every 12 hours).

Number of subjects in period 2[2]	DB sorafenib first, then option of OL sorafenib treatment	DB placebo first, then option of OL sorafenib treatment
Started	86	161
Completed	0	0
Not completed	86	161
Physician decision	1	-
Transferred to treatment continuation study	2	-
Adverse Event	20	30
Protocol driven decision point	1	1
Non-compliant with study medication	1	-
Progression, recurrence or relapse	40	82
Patient convenience	1	-
Transferred to treat. continuation study	-	3
Consent withdrawn by subject	6	21
Switched to commercial drug	6	7
Death	7	15
Lost to follow-up	1	1
Target lesion removed	-	1

Notes:

[2] - 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: Not all enrolled subjects received treatment. Only treated subjects were included in the baseline period.

Period 3

Period 3 title	Long term follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	DB sorafenib first, then option of OL sorafenib treatment
Arm description:	
Participants entered long-term follow-up if terminated double-blind or open-label periods	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	DB placebo first, then option of OL sorafenib treatment
Arm description:	
Participants entered long-term follow-up if terminated double-blind or open-label periods	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	DB sorafenib first, then option of OL sorafenib treatment	DB placebo first, then option of OL sorafenib treatment
Started	72	124
Completed	3	4
Not completed	69	120
Consent withdrawn by subject	8	14
Switched to commercial drug	4	2
Transferred to treatment continuation study	-	3
Disease program, recurrence or relapse	-	1
Protocol driven decision point	25	26
Death	27	68
Lost to follow-up	3	6
Transferred to treat. continuation study	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006)
Reporting group description:	
Participants received 2 tablets of Sorafenib (2×200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle	
Reporting group title	Placebo
Reporting group description:	
Participants received 2 tablets of Sorafenib-matching placebo orally twice daily (12 hours apart without food), 28 days comprise a cycle	

Reporting group values	Sorafenib (Nexavar, BAY43-9006)	Placebo	Total
Number of subjects	207	210	417
Age categorical			
Units: Subjects			
< 60 years	80	81	161
>= 60 years	127	129	256
Age continuous			
Units: years			
median	61.5	62.0	
standard deviation	± 11.2	± 11.7	-
Gender categorical			
Units: Subjects			
Female	103	115	218
Male	104	95	199
Geographic region			
Units: Subjects			
Europe	124	125	249
North America	36	36	72
Asia	47	49	96
ECOG (Eastern Cooperative Oncology Group)			
The ECOG PS required for the study was 0 (fully active), 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), or 2 (ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours).			
Units: Subjects			
Missing	1	1	2
Zero	130	129	259
One	69	74	143
Two	7	6	13

End points

End points reporting groups

Reporting group title	Sorafenib (Nexavar, BAY43-9006)
Reporting group description:	
Participants received 2 tablets of Sorafenib (2×200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle	
Reporting group title	Placebo
Reporting group description:	
Participants received 2 tablets of Sorafenib-matching placebo orally twice daily (12 hours apart without food), 28 days comprise a cycle	
Reporting group title	DB sorafenib first, then option of OL sorafenib treatment
Reporting group description:	
Participants received 2 tablets of Sorafenib (2×200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle.	
Reporting group title	DB placebo first, then option of OL sorafenib treatment
Reporting group description:	
Participants on placebo who switched to sorafenib, received sorafenib 400 mg (2 x 200 mg) orally twice daily, 28 days comprise a cycle.	
Reporting group title	DB sorafenib first, then option of OL sorafenib treatment
Reporting group description:	
Participants entered long-term follow-up if terminated double-blind or open-label periods	
Reporting group title	DB placebo first, then option of OL sorafenib treatment
Reporting group description:	
Participants entered long-term follow-up if terminated double-blind or open-label periods	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS). The primary population for efficacy analysis was the FAS. The FAS was identical to the intent-to-treat (ITT) population, which was defined as all randomized participants. Participants were analyzed as randomized.	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol set (PPS). A participant was included in the PPS if he/she was randomized and was evaluable for tumor response based on imaging data, had exposure to study medication, and had no major protocol deviations.	
Subject analysis set title	Pharmacokinetic (PK) analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic (PK) analysis set=participants with PK data collected after 14 days of uninterrupted and unmodified dosing of sorafenib. If an interruption occurred within 14 days prior to the sample, no doses may be missed for 3 days prior to the sample, and no more than 3 doses could be missed 4 to 14 days prior to the sample collection date.	

Primary: Progression-free survival (PFS) based on central assessment incl. clinical progression due to bone irradiation

End point title	Progression-free survival (PFS) based on central assessment incl. clinical progression due to bone irradiation
End point description:	
PFS=time from randomization to first observed disease progression (radiological according to central assessment or clinical due to bone irradiation, whichever is earlier), or death due to any cause, if death occurred before progression. Progression was assessed by RECIST criteria, version 1.0, modified for bone lesions. PFS for participants without disease progression or death at the time of analysis or unblinding were censored at the last date of tumor assessment before unblinding. Participants with no tumor evaluation after baseline were censored at Day 1. PD (Progression Disease)=At least a 20%	

increase in sum of longest diameters (LD) of measured lesions taking as reference the smallest sum LD on study since the treatment started or the appearance of 1 or more new lesions. New lesions also constituted PD. In exceptional circumstances, unequivocal progression of a nonmeasured lesion may have been accepted as evidence of disease progression in participants with measurable disease.

End point type	Primary

End point timeframe:

Final analysis to be performed when approximately 267 progression-free survival events (centrally assessed) had occurred, study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[1]	210[2]		
Units: Days				
median (full range (min-max))	329 (278 to 393)	175 (160 to 238)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The two treatment groups were compared using a stratified one-sided log rank test with an overall alpha of 0.01 stratified by age group and region. The null hypothesis that both treatment arms have the same PFS distribution will be tested against the alternative hypothesis that the distribution of PFS times in the sorafenib arm is different from the control arm according to the Lehmann alternative, which is equivalent to the assumption of proportional hazards of the treatment arms.

Comparison groups	Placebo v Sorafenib (Nexavar, BAY43-9006)
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Log Rank

Statistical analysis title	Statistical Analysis 2
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.587
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.454
upper limit	0.758

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival was defined as the time (days) from date of randomization to date of death due to any cause. Subjects still alive at the time of analysis were censored at their date of last contact. Since the median value could not be estimated due to censored data, the percentage of participants who died is presented.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (30 AUG 2017), study duration approximately eight years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[3]	210[4]		
Units: Percentage of participants				
number (not applicable)	52.7	54.8		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2892
Method	Logrank

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Sorafenib (Nexavar, BAY43-9006)
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.928
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.713
upper limit	1.208

Secondary: Time to progression (TTP) based on central assessment incl. clinical progression due to bone irradiation

End point title	Time to progression (TTP) based on central assessment incl. clinical progression due to bone irradiation

End point description:

Time to progression was defined at the time (days) from randomization to progression (based on central assessment [radiological and clinical progression due to bone irradiation])

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (31 Aug 2012), study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[5]	210[6]		
Units: days				
median (full range (min-max))	337 (283 to 451)	175 (160 to 238)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank

Statistical analysis title	Statistical Analysis 2
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.557

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.429
upper limit	0.724

Secondary: Disease control rate (DCR) based on central assessment

End point title	Disease control rate (DCR) based on central assessment

End point description:

Disease control rate was defined as the proportion of subjects whose best response was complete response (CR), partial response (PR), or stable disease (SD). Per Response Evaluation Criteria in Solid Tumors (RECIST) criteria, CR and PR were to be confirmed by another scan at least 4 weeks later; SD had to be documented at least 4 weeks after date of randomization. CR = Disappearance of all clinical and radiological evidence of tumor (both target and no-target). PR = At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum. SD = steady state of disease which is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (31 Aug 2012), study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196[7]	201[8]		
Units: Percentage of participants				
median (full range (min-max))	86.2 (80.6 to 90.7)	74.6 (68.0 to 80.5)		

Notes:

[7] - PPS

[8] - PPS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0015
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of response rates
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	19.4

Secondary: Response rate based on central assessment

End point title	Response rate based on central assessment

End point description:

Response rate was defined as the proportion of subjects whose best response was CR or PR. Per RECIST, CR and PR was to be confirmed by another scan at least 4 weeks later. CR = Disappearance of all clinical and radiological evidence of tumor (both target and no-target). PR = At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (31 Aug 2012), study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196[9]	201[10]		
Units: Percentage of participants				
median (full range (min-max))	12.24 (8.01 to 17.67)	0.5 (0.01 to 2.74)		

Notes:

[9] - PPS

[10] - PPS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	16.5

Secondary: Duration of response (DOR) based on central assessment

End point title	Duration of response (DOR) based on central assessment

End point description:

Duration of response was defined as the time from the first documented objective response of PR or CR,

whichever was noted earlier, to disease progression or death (if death occurred before progression was documented). CR = Disappearance of all clinical and radiological evidence of tumor (both target and no-target). PR = At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (31 Aug 2012), study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[11]	1[12]		
Units: days				
median (full range (min-max))	309 (226 to 505)	99999 (99999 to 99999)		

Notes:

[11] - FAS

[12] - only one subject with PR.
99999 stands for NA.
FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum percent reduction in target lesion size based on central assessment

End point title	Maximum percent reduction in target lesion size based on central assessment

End point description:

The magnitude of change from baseline in target lesion size in evaluable participants with scans was determined.

End point type	Secondary

End point timeframe:

From randomization of the first subject until the database cut-off (31 Aug 2012), study duration approximately three years

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196[13]	201[14]		
Units: Percentage of participants				
number (not applicable)				
Reduction ≥ 30%	17.3	1.0		
Reduction ≥ 20% but < 30%	15.3	1.5		
Reduction ≥ 10% but < 20%	22.4	3.5		
Reduction > 0% but < 10%	22.4	21.9		
Growth ≥ 0%	12.8	62.7		

Not assessed	9.7	9.5		

Notes:

[13] - PPS

[14] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-12h),ss (area under the concentration time curve from time 0 to 12 hours at steady state)

End point title	AUC(0-12h),ss (area under the concentration time curve from time 0 to 12 hours at steady state)[15]

End point description:

Sorafenib AUC(0-12h),ss (area under the concentration time curve from time 0 to 12 hours at steady state) was estimated from the steady state plasma concentration.

End point type	Secondary

End point timeframe:

A single pharmacokinetic plasma sample was collected at steady state (after 14 days of uninterrupted, unmodified sorafenib dosing)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only subjects who received sorafenib treatment in double blind period were included in PK analysis.

End point values	Sorafenib (Nexavar, BAY43-9006)			
Subject group type	Reporting group			
Number of subjects analysed	113[16]			
Units: mg*h/L				
geometric mean (standard deviation)	75.4 (± 1.5)			

Notes:

[16] - Pharmacokinetic (PK) analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After signing the informed consent until the database cut-off 30 AUG 2017, study duration approximately eight years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Sorafenib (Double Blind Only)

Reporting group description:

Reporting Group 1: Participants received 2 tablets of Sorafenib (2x200 mg) orally twice daily (12 hours apart without food), 28 days comprise a cycle. Data were collected from randomization to the end of double blind period

Reporting group title	Placebo (Double Blind Only)

Reporting group description:

Reporting Group 2: Participants received 2 tablets of Sorafenib-matching placebo orally twice daily (12 hours apart without food), 28 days comprise a cycle. Data were collected from randomization to the end of double-blind period.

Reporting group title	Sorafenib, Open Label Only (Sorafenib continued)

Reporting group description:

Reporting Group 3: Participants on sorafenib who continued OL sorafenib treat., received sorafenib 400 mg (2 x 200 mg) orally twice daily, 28 days comprise a cycle. Data were collected from the start of OL period to the data cutoff on 31 Aug

Reporting group title	Placebo, Open Label Only (Switch to Sorafenib)

Reporting group description:

Reporting Group 3: Participants on placebo who switched to sorafenib, received sorafenib 400 mg (2 x 200 mg) orally twice daily, 28 days comprise a cycle. Data were collected from the start of open label period to the data cutoff on 31 Aug 20

Serious adverse events	Sorafenib (Double Blind Only)	Placebo (Double Blind Only)	Sorafenib, Open Label Only (Sorafenib continued)
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 207 (42.03%)	58 / 209 (27.75%)	51 / 86 (59.30%)
number of deaths (all causes)	71	25	38
number of deaths resulting from adverse events	14	8	9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy (possibly related to cancer treatment)			
subjects affected / exposed	11 / 207 (5.31%)	6 / 209 (2.87%)	4 / 86 (4.65%)
occurrences causally related to treatment / all	5 / 13	1 / 6	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

CNS hemorrhage			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematoma			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hemorrhage - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage pulmonary, Bronchopulmonary NOS			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage pulmonary, Bronchus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage pulmonary, Larynx			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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 pulmonary, Lung			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage pulmonary, Respiratory tract NOS			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Anus			

subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Colon			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GI, Varices (rectal)			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Urinary NOS			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, GU, Uterus			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis/Embolism (vascular access)			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Thrombosis/Thrombus/Embolism			
subjects affected / exposed	1 / 207 (0.48%)	4 / 209 (1.91%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Vascular - Other			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Constitutional symptoms - Other			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Death not associated with CTCAE term, Death NOS			
subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	2 / 3	0 / 0	1 / 1
Death not associated with CTCAE term, Disease progression NOS			
subjects affected / exposed	2 / 207 (0.97%)	2 / 209 (0.96%)	3 / 86 (3.49%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	2 / 2	2 / 2	3 / 3
Death not associated with CTCAE term, Multi-Organ Failure			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Death not associated with CTCAE term, Sudden death			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Fatigue			
subjects affected / exposed	3 / 207 (1.45%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	4 / 207 (1.93%)	0 / 209 (0.00%)	0 / 86 (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
Flu-like syndrome			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

No code in CTCAE			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Not coded yet			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pain, Abdomen NOS			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Back			
subjects affected / exposed	1 / 207 (0.48%)	2 / 209 (0.96%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Bone			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Chest wall			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Chest/Thorax NOS			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Dental/Teeth/peridontal			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Extremity - limb			

subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Head/Headache			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
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, Joint			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Liver			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
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, Lymph node			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Neuralgia/Peripheral nerve			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Pelvis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Stomach			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Throat/Pharynx/Larynx			

subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain, Tumor pain			
subjects affected / exposed	2 / 207 (0.97%)	2 / 209 (0.96%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syndromes - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tumor flare			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight loss			
subjects affected / exposed	2 / 207 (0.97%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergy - Other			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Reproductive system and breast disorders			
Sexual - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Airway obstruction, Larynx			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Airway obstruction, Pharynx			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Airway obstruction, Trachea			
subjects affected / exposed	3 / 207 (1.45%)	3 / 209 (1.44%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea (Shortness of breath)			
subjects affected / exposed	8 / 207 (3.86%)	7 / 209 (3.35%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 9	0 / 8	0 / 2
deaths causally related to treatment / all	2 / 2	2 / 2	1 / 1
Hypoxia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Pleural effusion			
subjects affected / exposed	6 / 207 (2.90%)	4 / 209 (1.91%)	9 / 86 (10.47%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 13
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary - Other			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intraop injury, Artery-aorta			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Intraop injury, Bone			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Intraop injury, Meninges			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraop injury, Neck NOS			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraop injury, Thyroid			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraop injury, Trachea			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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 disorders			
Cardiac arrhythmia - Other			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac general - Other			
subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ischemia/infarction			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary arrest			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Pericardial effusion			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular arrhythmia, Atrial fibrillation			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular arrhythmia, Atrial flutter			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular arrhythmia, Supraventricular tachycardia			

subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Valvular heart disease			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia, Ventricular tachycardia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CNS ischemia			
subjects affected / exposed	3 / 207 (1.45%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CSF leak			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disturbance			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal nerve			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood Alteration, Anxiety			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood alteration, Depression			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Neurology - Other			
subjects affected / exposed	1 / 207 (0.48%)	2 / 209 (0.96%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy: Cranial, CN II Vision			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Neuropathy: motor			
subjects affected / exposed	0 / 207 (0.00%)	3 / 209 (1.44%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy: sensory			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope (Fainting)			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Blood and lymphatic system disorders			
Blood - Other			

subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemoglobin			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	0 / 86 (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
Lymphatics - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophils			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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			
Cataract			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Ocular - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic disc edema			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Anorexia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Colitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Dehydration			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Dysphagia			
subjects affected / exposed	2 / 207 (0.97%)	1 / 209 (0.48%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula, GI, Abdomen NOS			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Esophagus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GI - Other			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis (functional/symptomatic), Oral cavity			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Mucositis (functional/symptomatic), Trachea			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GI, Esophagus			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Gallbladder			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stricture, GI, Esophagus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Teeth			

subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer, GI, Rectum			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary - Other			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Liver dysfunction			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Pancreatitis			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	0 / 86 (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
Skin and subcutaneous tissue disorders			
Dermatology - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand-foot skin reaction			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Rash/desquamation			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	0 / 86 (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
Ulceration			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication, non-infectious			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal - Other			
subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	0 / 86 (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
Urinary retention			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Endocrine disorders			
Endocrine - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthritis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Extremity - upper (Function)			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	4 / 207 (1.93%)	6 / 209 (2.87%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spine ROM			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness, Extremity - lower			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness, Extremity - upper			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
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	4 / 207 (1.93%)	3 / 209 (1.44%)	5 / 86 (5.81%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Colitis, infectious			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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), Lung (Pneumonia)			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infection (Documented clinically), Soft tissue NOS			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (Documented clinically), Upper airway NOS			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
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 (Documented clinically), Wound			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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	0 / 207 (0.00%)	0 / 209 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Anal/perianal			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Bladder (urinary)			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Blood			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Bone (Osteomyelitis)			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Colon			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Kidney			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 207 (0.48%)	2 / 209 (0.96%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Mediastinum NOS			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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, Scrotum			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Soft			

tissue NOS			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Upper airway NOS			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	0 / 86 (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 normal ANC, Urinary tract NOS			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with normal ANC, Wound			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
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 unknown ANC, Abdomen NOS			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Appendix			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Bladder (urinary)			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Blood			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infection with unknown ANC, Bronchus			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 207 (0.48%)	1 / 209 (0.48%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Infection with unknown ANC, Pleura (Empyema)			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection with unknown ANC, Prostate			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Opportunistic infection			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Amylase			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Creatinine			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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

Hypercalcemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Hypomagnesemia			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	0 / 86 (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
Metabolic/Lab - Other			
subjects affected / exposed	0 / 207 (0.00%)	0 / 209 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo, Open Label Only (Switch to Sorafenib)		
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 161 (59.63%)		
number of deaths (all causes)	90		
number of deaths resulting from adverse events	23		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary malignancy (possibly related to cancer treatment)			

subjects affected / exposed	3 / 161 (1.86%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
CNS hemorrhage			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hematoma			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemorrhage - Other			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Hemorrhage pulmonary, Bronchopulmonary NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemorrhage pulmonary, Bronchus			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemorrhage pulmonary, Larynx			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemorrhage pulmonary, Lung			
subjects affected / exposed	3 / 161 (1.86%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	1 / 1		
Hemorrhage pulmonary, Respiratory tract NOS			

subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, GI, Anus				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, GI, Colon				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, GI, Varices (rectal)				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, GU, Urinary NOS				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, GU, Uterus				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis/Embolism (vascular access)				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis/Thrombus/Embolism				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular - Other				

subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Constitutional symptoms - Other			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Death not associated with CTCAE term, Death NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death not associated with CTCAE term, Disease progression NOS			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	9 / 9		
Death not associated with CTCAE term, Multi-Organ Failure			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Death not associated with CTCAE term, Sudden death			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			

subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flu-like syndrome				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
No code in CTCAE				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Not coded yet				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Abdomen NOS				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Back				
subjects affected / exposed	4 / 161 (2.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pain, Bone				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain, Chest wall				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pain, Chest/Thorax NOS				

subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Dental/Teeth/peridontal				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Extremity - limb				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Head/Headache				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Joint				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Liver				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Lymph node				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Neuralgia/Peripheral nerve				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Pelvis				

subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Stomach				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain, Throat/Pharynx/Larynx				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain, Tumor pain				
subjects affected / exposed	3 / 161 (1.86%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Syndromes - Other				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumor flare				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight loss				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Allergic reaction				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Allergy - Other				

subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Sexual - Other			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Airway obstruction, Larynx			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Airway obstruction, Pharynx			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Airway obstruction, Trachea			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnea (Shortness of breath)			
subjects affected / exposed	8 / 161 (4.97%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	2 / 2		
Hypoxia			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pleural effusion				
subjects affected / exposed	5 / 161 (3.11%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	3 / 3			
Pneumonitis				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary - Other				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
Injury, poisoning and procedural complications				
Intraop injury, Artery-aorta				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraop injury, Bone				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraop injury, Meninges				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intraop injury, Neck NOS				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Intraop injury, Thyroid				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intraop injury, Trachea				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrhythmia - Other				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac general - Other				
subjects affected / exposed	4 / 161 (2.48%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	1 / 1			
Cardiac ischemia/infarction				
subjects affected / exposed	3 / 161 (1.86%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	1 / 1			
Cardiopulmonary arrest				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular arrhythmia, Atrial fibrillation				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Supraventricular arrhythmia, Atrial flutter				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular arrhythmia, Supraventricular tachycardia				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Valvular heart disease				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia, Ventricular tachycardia				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CNS ischemia				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 1			
CSF leak				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cognitive disturbance				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				

subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal nerve				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mood Alteration, Anxiety				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mood alteration, Depression				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurology - Other				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuropathy: Cranial, CN II Vision				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy: motor				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuropathy: sensory				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope (Fainting)			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood - Other			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hemoglobin			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Lymphatics - Other			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophils			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ocular - Other			

subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Optic disc edema				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Anorexia				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 161 (1.24%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhea				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fistula, GI, Abdomen NOS				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fistula, GI, Esophagus				

subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GI - Other				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucositis (functional/symptomatic), Oral cavity				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucositis (functional/symptomatic), Trachea				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction, GI, Esophagus				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction, GI, Gallbladder				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perforation, GI, Colon				

subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stricture, GI, Esophagus				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Teeth				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcer, GI, Rectum				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary - Other				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver dysfunction				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatology - Other			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hand-foot skin reaction			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash/desquamation			
subjects affected / exposed	3 / 161 (1.86%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Ulceration			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound complication, non-infectious			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal - Other			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Endocrine - Other				
subjects affected / exposed	3 / 161 (1.86%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity - upper (Function)				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	4 / 161 (2.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Lumbar spine ROM				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle weakness, Extremity - lower				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle weakness, Extremity - upper				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Muscle weakness, Whole body/generalized				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal - Other				
subjects affected / exposed	4 / 161 (2.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Colitis, infectious				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection (Documented clinically), Lung (Pneumonia)				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection (Documented clinically), Soft tissue NOS				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection (Documented clinically), Upper airway NOS				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection (Documented clinically), Wound				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection - Other				

subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Anal/perianal			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Bladder (urinary)			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Blood			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Bone (Osteomyelitis)			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Colon			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Kidney			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Lung (Pneumonia)			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Infection with normal ANC, Mediastinum NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Scrotum			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Soft tissue NOS			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Upper airway NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Urinary tract NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC, Wound			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with unknown ANC, Abdomen NOS			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection with unknown ANC, Appendix			

subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown ANC, Bladder (urinary)				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown ANC, Blood				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown ANC, Bronchus				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown ANC, Lung (Pneumonia)				
subjects affected / exposed	3 / 161 (1.86%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
Infection with unknown ANC, Pleura (Empyema)				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown ANC, Prostate				
subjects affected / exposed	0 / 161 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Opportunistic infection				
subjects affected / exposed	1 / 161 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Metabolism and nutrition disorders			
Amylase			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Creatinine			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcemia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycemia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcemia			
subjects affected / exposed	0 / 161 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesemia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic/Lab - Other			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sorafenib (Double Blind Only)	Placebo (Double Blind Only)	Sorafenib, Open Label Only (Sorafenib continued)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 207 (97.58%)	173 / 209 (82.78%)	74 / 86 (86.05%)
Vascular disorders			
Hemorrhage pulmonary, Nose			
subjects affected / exposed	15 / 207 (7.25%)	2 / 209 (0.96%)	2 / 86 (2.33%)
occurrences (all)	17	3	2
Cardiac disorders			
Hypertension			
subjects affected / exposed	85 / 207 (41.06%)	28 / 209 (13.40%)	10 / 86 (11.63%)
occurrences (all)	103	35	13
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 207 (6.76%)	7 / 209 (3.35%)	1 / 86 (1.16%)
occurrences (all)	17	8	1
Mood Alteration, Anxiety			
subjects affected / exposed	7 / 207 (3.38%)	6 / 209 (2.87%)	0 / 86 (0.00%)
occurrences (all)	8	6	0
Neuropathy: sensory			
subjects affected / exposed	32 / 207 (15.46%)	13 / 209 (6.22%)	5 / 86 (5.81%)
occurrences (all)	42	16	6
Blood and lymphatic system disorders			
Blood - Other			
subjects affected / exposed	6 / 207 (2.90%)	6 / 209 (2.87%)	6 / 86 (6.98%)
occurrences (all)	6	10	20
Edema: Limb			
subjects affected / exposed	13 / 207 (6.28%)	6 / 209 (2.87%)	8 / 86 (9.30%)
occurrences (all)	17	7	9
Hemoglobin			
subjects affected / exposed	18 / 207 (8.70%)	10 / 209 (4.78%)	8 / 86 (9.30%)
occurrences (all)	24	11	9
Leukocytes			

subjects affected / exposed	9 / 207 (4.35%)	4 / 209 (1.91%)	5 / 86 (5.81%)
occurrences (all)	13	8	6
Lymphopenia			
subjects affected / exposed	7 / 207 (3.38%)	6 / 209 (2.87%)	1 / 86 (1.16%)
occurrences (all)	7	8	1
Platelets			
subjects affected / exposed	8 / 207 (3.86%)	2 / 209 (0.96%)	3 / 86 (3.49%)
occurrences (all)	12	2	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	102 / 207 (49.28%)	52 / 209 (24.88%)	19 / 86 (22.09%)
occurrences (all)	132	58	23
Fever			
subjects affected / exposed	22 / 207 (10.63%)	10 / 209 (4.78%)	8 / 86 (9.30%)
occurrences (all)	30	11	10
Flu-like syndrome			
subjects affected / exposed	18 / 207 (8.70%)	10 / 209 (4.78%)	4 / 86 (4.65%)
occurrences (all)	32	14	5
Insomnia			
subjects affected / exposed	14 / 207 (6.76%)	6 / 209 (2.87%)	5 / 86 (5.81%)
occurrences (all)	16	6	5
Pain, Abdomen NOS			
subjects affected / exposed	30 / 207 (14.49%)	10 / 209 (4.78%)	6 / 86 (6.98%)
occurrences (all)	42	10	7
Pain, Back			
subjects affected / exposed	24 / 207 (11.59%)	21 / 209 (10.05%)	10 / 86 (11.63%)
occurrences (all)	28	24	11
Pain, Bone			
subjects affected / exposed	14 / 207 (6.76%)	18 / 209 (8.61%)	7 / 86 (8.14%)
occurrences (all)	21	22	12
Pain, Chest wall			
subjects affected / exposed	6 / 207 (2.90%)	3 / 209 (1.44%)	2 / 86 (2.33%)
occurrences (all)	8	3	2
Pain, Chest/Thorax NOS			

subjects affected / exposed	16 / 207 (7.73%)	5 / 209 (2.39%)	1 / 86 (1.16%)
occurrences (all)	20	5	1
Pain, Dental/Teeth/peridontal			
subjects affected / exposed	11 / 207 (5.31%)	4 / 209 (1.91%)	2 / 86 (2.33%)
occurrences (all)	15	4	2
Pain, Extremity - limb			
subjects affected / exposed	31 / 207 (14.98%)	19 / 209 (9.09%)	3 / 86 (3.49%)
occurrences (all)	49	27	3
Pain, Head/Headache			
subjects affected / exposed	38 / 207 (18.36%)	16 / 209 (7.66%)	3 / 86 (3.49%)
occurrences (all)	48	17	3
Pain, Joint			
subjects affected / exposed	20 / 207 (9.66%)	14 / 209 (6.70%)	5 / 86 (5.81%)
occurrences (all)	23	19	7
Pain, Muscle			
subjects affected / exposed	19 / 207 (9.18%)	15 / 209 (7.18%)	6 / 86 (6.98%)
occurrences (all)	23	17	6
Pain, Neck			
subjects affected / exposed	9 / 207 (4.35%)	6 / 209 (2.87%)	1 / 86 (1.16%)
occurrences (all)	10	6	1
Pain, Oral cavity			
subjects affected / exposed	7 / 207 (3.38%)	2 / 209 (0.96%)	0 / 86 (0.00%)
occurrences (all)	7	2	0
Pain, Other			
subjects affected / exposed	24 / 207 (11.59%)	16 / 209 (7.66%)	8 / 86 (9.30%)
occurrences (all)	30	17	13
Pain, Throat/Pharynx/Larynx			
subjects affected / exposed	21 / 207 (10.14%)	9 / 209 (4.31%)	1 / 86 (1.16%)
occurrences (all)	26	11	3
Weight loss			
subjects affected / exposed	102 / 207 (49.28%)	29 / 209 (13.88%)	29 / 86 (33.72%)
occurrences (all)	114	30	33
Immune system disorders			
Rhinitis			
subjects affected / exposed	9 / 207 (4.35%)	7 / 209 (3.35%)	2 / 86 (2.33%)
occurrences (all)	11	10	2

Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	67 / 207 (32.37%)	12 / 209 (5.74%)	7 / 86 (8.14%)
occurrences (all)	89	12	9
Constipation			
subjects affected / exposed	32 / 207 (15.46%)	18 / 209 (8.61%)	4 / 86 (4.65%)
occurrences (all)	38	19	4
Diarrhea			
subjects affected / exposed	142 / 207 (68.60%)	32 / 209 (15.31%)	22 / 86 (25.58%)
occurrences (all)	226	40	26
Dry mouth			
subjects affected / exposed	16 / 207 (7.73%)	8 / 209 (3.83%)	2 / 86 (2.33%)
occurrences (all)	16	8	2
Dysphagia			
subjects affected / exposed	14 / 207 (6.76%)	9 / 209 (4.31%)	5 / 86 (5.81%)
occurrences (all)	17	9	7
GI - Other			
subjects affected / exposed	9 / 207 (4.35%)	4 / 209 (1.91%)	2 / 86 (2.33%)
occurrences (all)	11	4	3
Heartburn			
subjects affected / exposed	10 / 207 (4.83%)	10 / 209 (4.78%)	1 / 86 (1.16%)
occurrences (all)	11	10	1
Mucositis (functional/symptomatic), Oral cavity			
subjects affected / exposed	49 / 207 (23.67%)	7 / 209 (3.35%)	6 / 86 (6.98%)
occurrences (all)	58	7	14
Nausea			
subjects affected / exposed	43 / 207 (20.77%)	25 / 209 (11.96%)	10 / 86 (11.63%)
occurrences (all)	55	29	12
Taste Alteration			
subjects affected / exposed	16 / 207 (7.73%)	0 / 209 (0.00%)	1 / 86 (1.16%)
occurrences (all)	16	0	1
Vomiting			
subjects affected / exposed	23 / 207 (11.11%)	13 / 209 (6.22%)	3 / 86 (3.49%)
occurrences (all)	36	14	3
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	34 / 207 (16.43%)	34 / 209 (16.27%)	9 / 86 (10.47%)
occurrences (all)	43	39	10
Dyspnea (Shortness of breath)			
subjects affected / exposed	31 / 207 (14.98%)	27 / 209 (12.92%)	10 / 86 (11.63%)
occurrences (all)	36	32	14
Pulmonary - Other			
subjects affected / exposed	7 / 207 (3.38%)	7 / 209 (3.35%)	7 / 86 (8.14%)
occurrences (all)	8	7	11
Voice changes			
subjects affected / exposed	25 / 207 (12.08%)	6 / 209 (2.87%)	2 / 86 (2.33%)
occurrences (all)	33	6	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	141 / 207 (68.12%)	18 / 209 (8.61%)	4 / 86 (4.65%)
occurrences (all)	155	18	4
Dermatology - Other			
subjects affected / exposed	30 / 207 (14.49%)	6 / 209 (2.87%)	12 / 86 (13.95%)
occurrences (all)	56	8	14
Dry skin			
subjects affected / exposed	30 / 207 (14.49%)	12 / 209 (5.74%)	6 / 86 (6.98%)
occurrences (all)	36	14	7
Hand-foot skin reaction			
subjects affected / exposed	158 / 207 (76.33%)	20 / 209 (9.57%)	13 / 86 (15.12%)
occurrences (all)	223	24	15
Pruritus			
subjects affected / exposed	44 / 207 (21.26%)	22 / 209 (10.53%)	3 / 86 (3.49%)
occurrences (all)	52	24	6
Rash/desquamation			
subjects affected / exposed	107 / 207 (51.69%)	25 / 209 (11.96%)	9 / 86 (10.47%)
occurrences (all)	166	29	10
Musculoskeletal and connective tissue disorders			
Musculoskeletal - Other			
subjects affected / exposed	19 / 207 (9.18%)	9 / 209 (4.31%)	7 / 86 (8.14%)
occurrences (all)	21	9	10
Infections and infestations			

Infection - Other			
subjects affected / exposed	22 / 207 (10.63%)	12 / 209 (5.74%)	8 / 86 (9.30%)
occurrences (all)	29	19	11
Metabolism and nutrition disorders			
ALT			
subjects affected / exposed	26 / 207 (12.56%)	9 / 209 (4.31%)	0 / 86 (0.00%)
occurrences (all)	29	10	0
AST			
subjects affected / exposed	23 / 207 (11.11%)	5 / 209 (2.39%)	1 / 86 (1.16%)
occurrences (all)	26	6	2
Hypoalbuminemia			
subjects affected / exposed	2 / 207 (0.97%)	4 / 209 (1.91%)	5 / 86 (5.81%)
occurrences (all)	3	4	7
Hypocalcemia			
subjects affected / exposed	38 / 207 (18.36%)	11 / 209 (5.26%)	12 / 86 (13.95%)
occurrences (all)	54	13	21
Hypokalemia			
subjects affected / exposed	14 / 207 (6.76%)	5 / 209 (2.39%)	4 / 86 (4.65%)
occurrences (all)	21	6	6
Hypophosphatemia			
subjects affected / exposed	7 / 207 (3.38%)	1 / 209 (0.48%)	0 / 86 (0.00%)
occurrences (all)	11	1	0
Metabolic/Lab - Other			
subjects affected / exposed	79 / 207 (38.16%)	37 / 209 (17.70%)	21 / 86 (24.42%)
occurrences (all)	123	50	34

Non-serious adverse events	Placebo, Open Label Only (Switch to Sorafenib)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	159 / 161 (98.76%)		
Vascular disorders			
Hemorrhage pulmonary, Nose			
subjects affected / exposed	8 / 161 (4.97%)		
occurrences (all)	11		
Cardiac disorders			
Hypertension			

subjects affected / exposed	51 / 161 (31.68%)		
occurrences (all)	57		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 161 (7.45%)		
occurrences (all)	13		
Mood Alteration, Anxiety			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences (all)	10		
Neuropathy: sensory			
subjects affected / exposed	21 / 161 (13.04%)		
occurrences (all)	26		
Blood and lymphatic system disorders			
Blood - Other			
subjects affected / exposed	10 / 161 (6.21%)		
occurrences (all)	23		
Edema: Limb			
subjects affected / exposed	8 / 161 (4.97%)		
occurrences (all)	11		
Hemoglobin			
subjects affected / exposed	26 / 161 (16.15%)		
occurrences (all)	32		
Leukocytes			
subjects affected / exposed	8 / 161 (4.97%)		
occurrences (all)	15		
Lymphopenia			
subjects affected / exposed	10 / 161 (6.21%)		
occurrences (all)	13		
Platelets			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	68 / 161 (42.24%)		
occurrences (all)	87		
Fever			

subjects affected / exposed	21 / 161 (13.04%)		
occurrences (all)	26		
Flu-like syndrome			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	14		
Insomnia			
subjects affected / exposed	16 / 161 (9.94%)		
occurrences (all)	17		
Pain, Abdomen NOS			
subjects affected / exposed	30 / 161 (18.63%)		
occurrences (all)	38		
Pain, Back			
subjects affected / exposed	15 / 161 (9.32%)		
occurrences (all)	19		
Pain, Bone			
subjects affected / exposed	12 / 161 (7.45%)		
occurrences (all)	13		
Pain, Chest wall			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences (all)	9		
Pain, Chest/Thorax NOS			
subjects affected / exposed	17 / 161 (10.56%)		
occurrences (all)	18		
Pain, Dental/Teeth/peridontal			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	16		
Pain, Extremity - limb			
subjects affected / exposed	28 / 161 (17.39%)		
occurrences (all)	43		
Pain, Head/Headache			
subjects affected / exposed	24 / 161 (14.91%)		
occurrences (all)	29		
Pain, Joint			
subjects affected / exposed	19 / 161 (11.80%)		
occurrences (all)	25		
Pain, Muscle			

subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	17		
Pain, Neck			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences (all)	9		
Pain, Oral cavity			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences (all)	11		
Pain, Other			
subjects affected / exposed	27 / 161 (16.77%)		
occurrences (all)	31		
Pain, Throat/Pharynx/Larynx			
subjects affected / exposed	19 / 161 (11.80%)		
occurrences (all)	24		
Weight loss			
subjects affected / exposed	75 / 161 (46.58%)		
occurrences (all)	85		
Immune system disorders			
Rhinitis			
subjects affected / exposed	9 / 161 (5.59%)		
occurrences (all)	10		
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	48 / 161 (29.81%)		
occurrences (all)	52		
Constipation			
subjects affected / exposed	27 / 161 (16.77%)		
occurrences (all)	29		
Diarrhea			
subjects affected / exposed	96 / 161 (59.63%)		
occurrences (all)	165		
Dry mouth			
subjects affected / exposed	7 / 161 (4.35%)		
occurrences (all)	7		
Dysphagia			

subjects affected / exposed	12 / 161 (7.45%)		
occurrences (all)	14		
GI - Other			
subjects affected / exposed	10 / 161 (6.21%)		
occurrences (all)	11		
Heartburn			
subjects affected / exposed	13 / 161 (8.07%)		
occurrences (all)	14		
Mucositis (functional/symptomatic), Oral cavity			
subjects affected / exposed	41 / 161 (25.47%)		
occurrences (all)	49		
Nausea			
subjects affected / exposed	52 / 161 (32.30%)		
occurrences (all)	56		
Taste Alteration			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	18 / 161 (11.18%)		
occurrences (all)	25		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 161 (14.29%)		
occurrences (all)	28		
Dyspnea (Shortness of breath)			
subjects affected / exposed	25 / 161 (15.53%)		
occurrences (all)	32		
Pulmonary - Other			
subjects affected / exposed	7 / 161 (4.35%)		
occurrences (all)	9		
Voice changes			
subjects affected / exposed	12 / 161 (7.45%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	96 / 161 (59.63%)		
occurrences (all)	103		
Dermatology - Other			
subjects affected / exposed	31 / 161 (19.25%)		
occurrences (all)	43		
Dry skin			
subjects affected / exposed	17 / 161 (10.56%)		
occurrences (all)	17		
Hand-foot skin reaction			
subjects affected / exposed	109 / 161 (67.70%)		
occurrences (all)	136		
Pruritus			
subjects affected / exposed	21 / 161 (13.04%)		
occurrences (all)	25		
Rash/desquamation			
subjects affected / exposed	67 / 161 (41.61%)		
occurrences (all)	94		
Musculoskeletal and connective tissue disorders			
Musculoskeletal - Other			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	16		
Infections and infestations			
Infection - Other			
subjects affected / exposed	12 / 161 (7.45%)		
occurrences (all)	17		
Metabolism and nutrition disorders			
ALT			
subjects affected / exposed	15 / 161 (9.32%)		
occurrences (all)	19		
AST			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	14		
Hypoalbuminemia			
subjects affected / exposed	7 / 161 (4.35%)		
occurrences (all)	7		

Hypocalcemia			
subjects affected / exposed	30 / 161 (18.63%)		
occurrences (all)	47		
Hypokalemia			
subjects affected / exposed	14 / 161 (8.70%)		
occurrences (all)	17		
Hypophosphatemia			
subjects affected / exposed	11 / 161 (6.83%)		
occurrences (all)	12		
Metabolic/Lab - Other			
subjects affected / exposed	56 / 161 (34.78%)		
occurrences (all)	101		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2009	Protocol amendment 1, dated 01 JUL 2009, introduced the following key changes: • Clarified ambiguous wording that did not take into account certain elements of clinical practice • Some inclusion criteria of the protocol were revised to allow enrollment of appropriate patients for the indication studied.
12 August 2009	Protocol amendment 2, 12 AUG 2009, implemented the US Food and Drug Administration's recommendations after the End-of-Phase-2 Meeting. These included: • A change in the definition of RAI refractory • Changes in secondary efficacy endpoints (to OS as the first secondary endpoint, and the addition of DoR as a secondary endpoint) • The measurement of total T3 instead of fT3 • Removal of the requirement for urine samples for pharmacogenetic biomarker analysis.
15 March 2010	Protocol amendment 4, 15 MAR 2010, revised the following: • The inclusion and exclusion criteria were updated to clarify contraception, pregnancy, and breastfeeding requirements • Specification of permitted doses of dexamethasone as well as consistency throughout the protocol of permitted/not-permitted concomitant medications was made. • A criterion for re-screening was added to specify how to handle subjects who had previously failed screening but were later eligible. • Study procedures were revised, including study removal criteria language, dose modifications, blood pressure measurements, cycle numbers and assessments, the requirement for FDG-PET scan at screening, and the study flow chart Revisions and additions were made in biomarkers and genetic testing.

09 December 2010	Protocol amendment 7, 09 DEC 2010, clarified or revised the following: • The definition of cycle length was redefined to the beginning of the cycle when the specific treatment course changes (e.g., when the blinded phase becomes the open-label phase) • An inclusion criterion was added to specify that subjects with poorly differentiated and other thyroid variants (eg, Insular, tall cell) were eligible for the study provided that the histology had no medullary differentiation nor anaplastic features. • Text was changed to specify that the use of biologic response modifiers were prohibited within 21 days of randomization, not 21 days of study entry. • Clarification was added to the inclusion criterion requiring subjects to have progression within 14 months that the progression was prior to 14 months of enrolment • In the definition of RAI refractory subjects in the inclusion criteria, specification was added that the post-radioactive-iodine scan could have been a diagnostic or therapeutic whole body scan. • An exception was added to the reason that subjects may be discontinued from study treatment if there is an interruption in study drug administration for more than 30 days (ie, if the interruption was due to PD that required interventions that precluded the use of sorafenib in the open-label phase [e.g., radiotherapy or surgery], the subject was permitted to continue on the study upon agreement between the investigator and the sponsor). • The dosing regimen and modifications to dosing were clarified. • Clarification on blood pressure monitoring of unblinded subjects was made. • Clarification on prior and concomitant therapy for long-term follow-up and survival subjects was made. • It was erroneously stated that the baseline CT/MRI scan was required prior to enrollment. It was corrected to state that the scan was required 28 days prior to randomization. (Continued)
09 December 2010	(Continued) Protocol amendment 7, 09 DEC 2010, clarified or revised the following: Text was added to allow up to 3 extra days added for randomization after signing informed consent in the event that the 28th day was on a weekend or was a holiday • A correction was made that study drug and the blood pressure monitoring form was distributed after randomization, not before. • Clarification was made that laboratory assessments were not required on day 1 of cycle 1 • Text was added to allow a subject who discontinued study drug, but did not progress, to continue with tumor assessments and survival assessments if he/she was in the long-term follow-up period • Clarification was added to specify that there is continued monitoring for subjects who discontinued study treatment but did not hit any study endpoint. • Clarification was made to the study flow chart that height was not required at the EOT visit and imaging tumor assessment were every 56 days during the follow-up.
24 August 2011	Protocol amendment 8, 24 AUG 2011, clarified or revised the following: • Increase the sample size of randomized subjects • Distinguish the primary endpoint analysis from the end of the study • Clarify that curable skin malignancies do not require removal from study • Clarify the definition of non-radiographically defined progression that can qualify for open-label crossover eligibility • Revise PK analysis methodology.
26 February 2013	Protocol amendment 9, 26 FEB 2013, clarified or revised the following: • Study procedures to be used following the primary completion date of the study, in order to enable subjects to receive treatment with sorafenib, if deemed appropriate by the investigator, and continue to be evaluated • Give subjects the opportunity to benefit from sorafenib treatment, minimize protocol deviations by clarification of procedures, and enable a more comprehensive evaluation of the efficacy of sorafenib for the treatment of thyroid cancer • Clarify the methods used to address the potential bias in the estimate of the treatment effect for OS due to crossover, with reference to the statistical analysis plan, as these correction methods would also be used for the follow-up OS analysis.

10 January 2014	Protocol amendment 10, 10 JAN 2014, revised and clarified the study procedures following the primary completion date of the study: • Lower the required tumor assessments from every 2 months to at the investigator's discretion, up to a threshold of at least one tumor assessment per year • Guidance for use of dose modification was added • Skin toxicity criteria were clarified to include that an occurrence can be any grade of the AE • Statistical analysis methodology for the event-driven overall survival analysis was added • Collection of the genetic plasma sample was removed • Text revised to state the AUCs would also be confirmed by population PK modelling.
21 July 2015	Protocol amendment 11, 21 JUL 2015, clarified or revised the following: • The Food and Drug Administration (FDA) agreed that it would be sufficient to conduct the final survival analysis with only 210 death events • Text was added indicating that the study will terminate when the final overall survival event number is reached • All subjects receiving clinical benefit of the study drug were assured to have continued access to it even beyond study closure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26370187

http://www.ncbi.nlm.nih.gov/pubmed/24768112

http://www.ncbi.nlm.nih.gov/pubmed/21834960