Clinical trial results:
A Phase III randomized, placebo controlled, double blind trial of Sorafenib plus Erlotinib vs. Sorafenib plus placebo as First Line systemic treatment for Hepatocellular Carcinoma (HCC)

Summary

EudraCT number	2008-006021-14
Trial protocol	DE ES GB BE FR IT BG AT GR
Global end of trial date	23 May 2018

Results information

Result version number	v1 (current)
This version publication date	01 June 2019
First version publication date	01 June 2019

Trial information

Trial identification

Sponsor protocol code	BAY43-9006/12917

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00901901
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	23 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: Overall Survival (OS) Secondary objectives: -Time to radiographic tumor progression (TTP) -Disease control rate (DCR) (proportion of subjects who had a best response rating of complete response [CR], partial response [PR], or stable disease [SD] according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria, that was maintained for at least 28 days from the first demonstration of that rating) -Safety -Health Related Quality of Life (HRQoL) and utility values as measured by the European Quality of life scale (5 dimensions) (EQ-5D)

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 Council for Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	China: 49
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	France: 76
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hong Kong: 11
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 20

Country: Number of subjects enrolled	Korea, Republic of: 49
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	United States: 88
Country: Number of subjects enrolled	South Africa: 10
Worldwide total number of subjects	720
EEA total number of subjects	308

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)	440
From 65 to 84 years	279
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 128 study centers in 26 countries in North America, South America, Europe, Africa, and Asia.

Pre-assignment

Screening details:

Of the 962 screened participants, 242 were screen failures and were excluded from participated in the study. A total of 720 participants were randomized to study arms: 358 participants in the sorafenib + placebo group and 362 participants in the sorafenib + erlotinib group.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

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

Arm description:

Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd)

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose was 150 mg once daily

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY 43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose was 400 mg twice a day

Arm title	Sorafenib (Nexavar, BAY43-9006) + Placebo

Arm description:

Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd)

Arm type	Experimental
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose was 150 mg once daily

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY 43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose was 400 mg twice a day

Number of subjects in period 1	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY43-9006) + Placebo
Started	362	358
Participants received treatment	362	355
Completed	193	181
Not completed	169	177
Consent withdrawn by subject	26	24
Physician decision	2	2
Adverse event, non-fatal	120	128
Protocol driven decision point	-	2
Switch to commercial drug	1	1
Study terminated by sponsor	2	-
Noncompliance with study medication	4	1
Transfer to treatment continuation study	5	2
Never treated	-	3
Lost to follow-up	3	5
Missing	1	-
Protocol deviation	5	9

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)
Reporting group description: Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd)	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Placebo
Reporting group description: Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd)	

Reporting group values	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY43-9006) + Placebo	Total
Number of subjects	362	358	720
Age categorical Units: Subjects			
In utero			0

Extrahepatic spread Units: Subjects			
Extrahepatic spread: Yes	205	219	424
Extrahepatic spread: No	157	139	296

Subject analysis sets	
Subject analysis set title	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd)	
Subject analysis set title	Sorafenib (Nexavar, BAY 43-9006) + Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd)	

Reporting group values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo	
Number of subjects	362	358	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	60.3	59.5	
standard deviation	± 11.8	± 13.0	
Sex: Female, Male Units: Subjects			
Female Male			
Smoking status Units: Subjects			
non-smoker former smoker current smoker			
ECOG stratification group			
Eastern Cooperative Oncology Group (ECOG) grade 0 = fully active; grade 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.			
Units: Subjects			
Grade 0 Grade 1			

Macroscopic vascular invasion Units: Subjects			
Macroscopic vascular invasion: Yes Macroscopic vascular invasion: No			
Extrahepatic spread Units: Subjects			
Extrahepatic spread: Yes Extrahepatic spread: No			

End points

End points reporting groups

Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)
Reporting group description:	
Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd)	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Placebo
Reporting group description:	
Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd)	
Subject analysis set title	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd)	
Subject analysis set title	Sorafenib (Nexavar, BAY 43-9006) + Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd)	

Primary: Overall survival

End point title	Overall survival
End point description:	
Overall Survival (OS) was defined as the time from date of randomization to death due to any cause.	
End point type	Primary
End point timeframe:	
From randomization of the first patient until 34 months or date of death of any cause whichever came first	

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Days				
median (confidence interval 95%)	289 (250 to 321)	259 (226 to 322)		

Statistical analyses

Statistical analysis title	Log rank test
Statistical analysis description:	
A one-sided log-rank test stratified by tumor burden, region, and ECOG at baseline was conducted.	
Comparison groups	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva) v Sorafenib (Nexavar, BAY 43-9006) + Placebo

Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.204
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9292
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7805
upper limit	1.1061

Secondary: Time to radiological tumor progression (TTP)

End point title	Time to radiological tumor progression (TTP)

End point description:

TTP was the time from randomization to radiological tumor progression. Participants without radiological tumor progression at the time of analysis were censored at their last date of tumor evaluation. Progressive disease (PD) was defined using Response Evaluation Criteria in Solid Tumors (RECIST version 1.0), as at least a 20% increase in the sum of longest diameter (LD) of measured lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. Appearance of new lesions also constituted PD.

End point type	Secondary

End point timeframe:

From randomization of the first participant until 34 months later (cut-off date), assessed every 6 weeks

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Days				
median (confidence interval 95%)	97 (82 to 126)	122 (88 to 136)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

End point title	Disease control

End point description:

Disease control was defined as the number of participants who had a best response rating of complete response (CR), partial response (PR), or stable disease (SD) according to RECIST assessed by magnetic resonance imaging (MRI) that was confirmed at least 28 days from the first demonstration of that

rating. CR: disappearance of all clinical and radiological evidence of target and non-target tumors. PR: at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. SD: steady state of disease. Neither sufficient shrinkage for PR nor sufficient increase for PD.

End point type	Secondary

End point timeframe:

From randomization of the first participant until 34 months later (cut-off date), assessed every 6 weeks

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Participants	159	188		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life and utility values as measured by EQ-5D - Index

End point title	Health-related quality of life and utility values as measured by EQ-5D - Index

End point description:

The European quality of life scale (5 dimensions) (EQ-5D) questionnaire was given to the participants at each visit. The EQ-5D questionnaire consisted of 5 ordinal categorical responses (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The scores for the EQ-5D dimensions are assigned according to the level of problems reported (1 'no problems'; 2 'some problems'; 3 'extreme problems'). The 5 health dimensions are summarized into a single score, the EQ-5D index score. The EQ-5D index score has a range of 0 and 1 with 0 representing death and 1 representing perfect health.

End point type	Secondary

End point timeframe:

The EQ-5D was administered at the beginning of the visit prior to seeing the investigator. Questionnaires were to be completed every 6 weeks (Day 1 of each cycle) for subsequent cycles and at the end of treatment visit.

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
cycle1	0.777 (0.760 to 0.795)	0.774 (0.757 to 0.790)		

cycle2	0.753 (0.735 to 0.771)	0.749 (0.732 to 0.766)		
cycle3	0.728 (0.708 to 0.748)	0.724 (0.706 to 0.743)		
cycle4	0.704 (0.681 to 0.726)	0.700 (0.678 to 0.721)		
cycle5	0.679 (0.653 to 0.705)	0.675 (0.650 to 0.700)		
cycle6	0.654 (0.625 to 0.684)	0.651 (0.622 to 0.679)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life and utility values as measured by EQ-5D - VAS

End point title	Health-related quality of life and utility values as measured by EQ-5D - VAS

End point description:

Participants indicated on a scale of 0 (worst) to 100 (best) how good or bad their health state was on that particular day.

End point type	Secondary

End point timeframe:

The EQ-5D VAS was administered at the beginning of the visit prior to seeing the investigator. Questionnaires were to be completed every 6 weeks (Day 1 of each cycle) for subsequent cycles and at the end of treatment visit.

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
cycle1	74.397 (73.219 to 75.576)	74.656 (73.504 to 75.808)		
cycle2	72.649 (71.420 to 73.877)	72.907 (71.735 to 74.080)		
cycle3	70.900 (69.518 to 72.281)	71.158 (69.854 to 72.462)		
cycle4	69.151 (67.542 to 70.759)	69.409 (67.891 to 70.927)		
cycle5	67.402 (65.520 to 69.283)	67.660 (65.875 to 69.445)		

cycle6	65.653 (63.468 to 67.837)	65.911 (63.827 to 67.996)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of response

End point title	Duration of response

End point description:

Duration of response - RECIST: number of days from the date that CR or PR is first documented to date that PD is first objectively documented or to death before progression. Note: the relevant date is that of the first documentation, not the confirmation date (if participant progressed or died then censored=no) or to last observation if participant did not progress or die then censored=yes note: this last observation date should be the same as that used for time to progression.

End point type	Other pre-specified

End point timeframe:

From randomization of the first participant until 34 months later (cut-off date), assessed every 6 weeks

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	14[1]		
Units: Days				
median (confidence interval 95%)	297 (100 to 427)	168 (90 to 99999)		

Notes:

[1] - For below CI: 99999 indicates that the upper bound of the CI was not available due to censored data.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to response

End point title	Time to response

End point description:

Time to response was the number of days from randomization to the date the CR or PR was documented (with confirmation) (Note: the relevant date is that of the first documentation, not the confirmation date).

End point type	Other pre-specified

End point timeframe:

From randomization of the first participant until 34 months later (cut-off date), assessed every 6 weeks

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	14		
Units: Days				
median (confidence interval 95%)	84.5 (47 to 122)	83.5 (39 to 331)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tumor response

End point title	Tumor response

End point description:

Tumor response was the proportion of participants with the best tumor response (ie, achieving either a confirmed complete response [CR] or partial response [PR], according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria).

End point type	Other pre-specified

End point timeframe:

From randomization of the first participant until 34 months later (cut-off date), assessed every 6 weeks

End point values	Sorafenib (Nexavar, BAY 43-9006) + Erlotinib (Tarceva)	Sorafenib (Nexavar, BAY 43-9006) + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	362	358		
Units: Participants	24	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of treatment up to 30 days after the last dose of study medication	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Placebo
Reporting group description: Participants received sorafenib 400 mg twice daily (bid) and matching erlotinib placebo 150 mg tablet once daily (qd).	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)
Reporting group description: Participants received sorafenib 400 mg twice daily (bid) and erlotinib 150 mg tablet once daily (qd).	

Serious adverse events	Sorafenib (Nexavar, BAY43-9006) + Placebo	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)	
Total subjects affected by serious adverse events			
subjects affected / exposed	198 / 355 (55.77%)	214 / 362 (59.12%)	
number of deaths (all causes)	271	258	
number of deaths resulting from adverse events	73	83	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy (possibly related to cancer treatment)			
subjects affected / exposed	2 / 355 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	3 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CNS hemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 2	
Hematoma			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemorrhage - Other			
subjects affected / exposed	4 / 355 (1.13%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Hemorrhage pulmonary, Bronchopulmonary NOS			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hemorrhage pulmonary, Nose			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage pulmonary, Respiratory tract NOS			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Abdomen NOS			
subjects affected / exposed	8 / 355 (2.25%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	1 / 10	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemorrhage with surgery			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemorrhage, GI, Anus			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Colon			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Duodenum			

subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Liver			
subjects affected / exposed	1 / 355 (0.28%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Hemorrhage, GI, Esophagus			
subjects affected / exposed	4 / 355 (1.13%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	2 / 4	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hemorrhage, GI, Lower GI NOS			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Oral cavity			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage, GI, Stomach			
subjects affected / exposed	4 / 355 (1.13%)	6 / 362 (1.66%)	
occurrences causally related to treatment / all	1 / 4	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemorrhage, GI, Upper GI NOS			
subjects affected / exposed	7 / 355 (1.97%)	11 / 362 (3.04%)	
occurrences causally related to treatment / all	3 / 9	1 / 13	
deaths causally related to treatment / all	0 / 1	0 / 3	
Hemorrhage, GI, Varices (esophageal)			
subjects affected / exposed	11 / 355 (3.10%)	6 / 362 (1.66%)	
occurrences causally related to treatment / all	6 / 18	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Hemorrhage, GI, Varices (rectal)			

subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0			

Constitutional Symptoms - Other			
subjects affected / exposed	19 / 355 (5.35%)	11 / 362 (3.04%)	
occurrences causally related to treatment / all	6 / 23	3 / 15	
deaths causally related to treatment / all	1 / 12	0 / 7	
Death not associated with CTCAE term, Death NOS			
subjects affected / exposed	1 / 355 (0.28%)	7 / 362 (1.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 7	
Death not associated with CTCAE term, Disease Progression NOS			
subjects affected / exposed	17 / 355 (4.79%)	18 / 362 (4.97%)	
occurrences causally related to treatment / all	1 / 17	0 / 18	
deaths causally related to treatment / all	1 / 17	0 / 18	
Death not associated with CTCAE term, Multi-Organ Failure			
subjects affected / exposed	3 / 355 (0.85%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 3	1 / 5	
Fatigue			
subjects affected / exposed	8 / 355 (2.25%)	11 / 362 (3.04%)	
occurrences causally related to treatment / all	12 / 15	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	11 / 355 (3.10%)	12 / 362 (3.31%)	
occurrences causally related to treatment / all	4 / 13	7 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu-like syndrome			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
No Code In CTCAE			
subjects affected / exposed	10 / 355 (2.82%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	2 / 11	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pain, Abdomen NOS			
subjects affected / exposed	15 / 355 (4.23%)	12 / 362 (3.31%)	
occurrences causally related to treatment / all	3 / 15	1 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Back			
subjects affected / exposed	3 / 355 (0.85%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Bone			
subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Chest wall			
subjects affected / exposed	0 / 355 (0.00%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Chest/thorax NOS			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Extremity - limb			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Joint			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Other (Specify)			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Muscle			

subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Pain NOS			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Scrotum			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Stomach			
subjects affected / exposed	0 / 355 (0.00%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain, Tumor pain			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syndromes - Other			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight gain			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea (shortness of breath)			

subjects affected / exposed	4 / 355 (1.13%)	7 / 362 (1.93%)	
occurrences causally related to treatment / all	0 / 8	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pleural effusion			
subjects affected / exposed	7 / 355 (1.97%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 8	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary - Other			
subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Intraop injury, Lung			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac General - Other			
subjects affected / exposed	3 / 355 (0.85%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ischemia/infarction			
subjects affected / exposed	4 / 355 (1.13%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 2	

Conduction abnormality, asystole			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertension			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 355 (0.56%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SupraVentricular arrhythmia, Atrial fibrillation			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SupraVentricular arrhythmia, Sinus bradycardia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SupraVentricular arrhythmia, Sinus tachycardia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular arrhythmia, Bigeminy			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS ischemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disturbance			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood Alteration, Agitation			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	6 / 355 (1.69%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	2 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	6 / 355 (1.69%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	5 / 8	7 / 16	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neuropathy: Cranial, CN V Motor-jaw muscles; Sensory-facial			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurology - Other			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mood Alteration, Depression			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy: motor			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	3 / 3	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy: sensory			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 355 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope (fainting)			
subjects affected / exposed	3 / 355 (0.85%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood - Other			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema: Limb			
subjects affected / exposed	4 / 355 (1.13%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemoglobin			
subjects affected / exposed	9 / 355 (2.54%)	8 / 362 (2.21%)	
occurrences causally related to treatment / all	8 / 15	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
INR			

subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophils			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelets			
subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular - Other			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	1 / 355 (0.28%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 1	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	13 / 355 (3.66%)	14 / 362 (3.87%)	
occurrences causally related to treatment / all	7 / 21	4 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 355 (1.41%)	12 / 362 (3.31%)	
occurrences causally related to treatment / all	1 / 5	6 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhea			
subjects affected / exposed	3 / 355 (0.85%)	15 / 362 (4.14%)	
occurrences causally related to treatment / all	4 / 4	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distension			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula, GI, Abdomen NOS			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula, GI, Anus			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula, GI, Stomach			

subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GI - Other			
subjects affected / exposed	4 / 355 (1.13%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastritis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heartburn			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 355 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (clinical exam), Large bowel			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (functional/symptomatic), Oral cavity			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis, GI, Colon/cecum/appendix			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction, GI, Colon			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction, GI, Gallbladder			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation, GI, Colon			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Perforation, GI, Duodenum			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Perforation, GI, Stomach			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Stricture, GI, Biliary tree			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer, GI, Duodenum			

subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer, GI, Stomach			
subjects affected / exposed	1 / 355 (0.28%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 355 (0.85%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary - Other			
subjects affected / exposed	8 / 355 (2.25%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver dysfunction			
subjects affected / exposed	30 / 355 (8.45%)	36 / 362 (9.94%)	
occurrences causally related to treatment / all	10 / 37	5 / 44	
deaths causally related to treatment / all	4 / 18	2 / 21	
Pancreatitis			
subjects affected / exposed	2 / 355 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 355 (0.00%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bruising			

subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	8 / 355 (2.25%)	10 / 362 (2.76%)	
occurrences causally related to treatment / all	1 / 13	3 / 12	
deaths causally related to treatment / all	1 / 3	0 / 4	
Urinary retention			
subjects affected / exposed	0 / 355 (0.00%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	0 / 355 (0.00%)	6 / 362 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness, Extremity - lower			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness, Whole body/generalized			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal - Other			
subjects affected / exposed	2 / 355 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Colitis, infectious			
subjects affected / exposed	0 / 355 (0.00%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection (Documented clinically), Biliary tree			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (Documented clinically), Bladder (urinary)			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (Documented clinically), Blood			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection (Documented clinically), Peritoneal Cavity			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection (Documented clinically), Lung (pneumonia)			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (Documented clinically), Skin (cellulitis)			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection - Other			
subjects affected / exposed	7 / 355 (1.97%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	1 / 7	0 / 5	
deaths causally related to treatment / all	1 / 2	0 / 1	
Infection with normal ANC, Abdomen NOS			

subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Blood			
subjects affected / exposed	3 / 355 (0.85%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infection with normal ANC, Anal/perianal			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Bronchus			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Catheter-related			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Heart (Endocarditis)			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Kidney			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Lung (pneumonia)			
subjects affected / exposed	1 / 355 (0.28%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	

Infection with normal ANC, Penis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Peritoneal cavity			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection with normal ANC, Skin (cellulitis)			
subjects affected / exposed	3 / 355 (0.85%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC, Upper airway NOS			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection with normal ANC, Urinary tract NOS			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC, Abdomen NOS			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC, Anal/perianal			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC, Biliary tree			

subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC, Blood			
subjects affected / exposed	1 / 355 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection with unknown ANC, Cornea			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC, Duodenum			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection with unknown ANC, Lung (pneumonia)			
subjects affected / exposed	2 / 355 (0.56%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Infection with unknown ANC, Peritoneal Cavity			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral hepatitis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ALT			
subjects affected / exposed	0 / 355 (0.00%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bilirubin (hyperbilirubinemia)			
subjects affected / exposed	5 / 355 (1.41%)	12 / 362 (3.31%)	
occurrences causally related to treatment / all	4 / 9	11 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
AST			
subjects affected / exposed	2 / 355 (0.56%)	6 / 362 (1.66%)	
occurrences causally related to treatment / all	2 / 3	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcemia			
subjects affected / exposed	2 / 355 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CPK			
subjects affected / exposed	1 / 355 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	3 / 355 (0.85%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	2 / 355 (0.56%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	1 / 355 (0.28%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia			

subjects affected / exposed	2 / 355 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphatemia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic/Lab - Other			
subjects affected / exposed	0 / 355 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sorafenib (Nexavar, BAY43-9006) + Placebo	Sorafenib (Nexavar, BAY43-9006) + Erlotinib (Tarceva)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	349 / 355 (98.31%)	353 / 362 (97.51%)	
Vascular disorders			
Hemorrhage pulmonary, Nose			
subjects affected / exposed	25 / 355 (7.04%)	63 / 362 (17.40%)	
occurrences (all)	48	123	
Cardiac disorders			
Hypertension			
subjects affected / exposed	86 / 355 (24.23%)	72 / 362 (19.89%)	
occurrences (all)	336	339	
Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 355 (7.04%)	18 / 362 (4.97%)	
occurrences (all)	45	52	
Mood Alteration, Depression			
subjects affected / exposed	23 / 355 (6.48%)	15 / 362 (4.14%)	
occurrences (all)	119	35	
Blood and lymphatic system disorders			
INR			

subjects affected / exposed	18 / 355 (5.07%)	19 / 362 (5.25%)	
occurrences (all)	56	36	
Hemoglobin			
subjects affected / exposed	49 / 355 (13.80%)	65 / 362 (17.96%)	
occurrences (all)	129	200	
Edema: Limb			
subjects affected / exposed	74 / 355 (20.85%)	82 / 362 (22.65%)	
occurrences (all)	150	176	
Leukocytes			
subjects affected / exposed	20 / 355 (5.63%)	17 / 362 (4.70%)	
occurrences (all)	41	48	
Platelets			
subjects affected / exposed	50 / 355 (14.08%)	45 / 362 (12.43%)	
occurrences (all)	186	156	
General disorders and administration site conditions			
Constitutional Symptoms - Other			
subjects affected / exposed	25 / 355 (7.04%)	21 / 362 (5.80%)	
occurrences (all)	53	33	
Fatigue			
subjects affected / exposed	192 / 355 (54.08%)	184 / 362 (50.83%)	
occurrences (all)	779	676	
Insomnia			
subjects affected / exposed	43 / 355 (12.11%)	36 / 362 (9.94%)	
occurrences (all)	105	151	
Fever			
subjects affected / exposed	64 / 355 (18.03%)	71 / 362 (19.61%)	
occurrences (all)	107	112	
Pain, Abdomen NOS			
subjects affected / exposed	112 / 355 (31.55%)	112 / 362 (30.94%)	
occurrences (all)	312	339	
Pain, Back			
subjects affected / exposed	48 / 355 (13.52%)	40 / 362 (11.05%)	
occurrences (all)	110	132	
Pain, Extremity - limb			

subjects affected / exposed	23 / 355 (6.48%)	15 / 362 (4.14%)	
occurrences (all)	74	46	
Pain, Chest/thorax NOS			
subjects affected / exposed	25 / 355 (7.04%)	10 / 362 (2.76%)	
occurrences (all)	47	15	
Pain, Head/headache			
subjects affected / exposed	51 / 355 (14.37%)	31 / 362 (8.56%)	
occurrences (all)	117	60	
Pain, Joint			
subjects affected / exposed	19 / 355 (5.35%)	24 / 362 (6.63%)	
occurrences (all)	48	56	
Weight loss			
subjects affected / exposed	111 / 355 (31.27%)	127 / 362 (35.08%)	
occurrences (all)	465	552	
Pain, Other (Specify)			
subjects affected / exposed	25 / 355 (7.04%)	20 / 362 (5.52%)	
occurrences (all)	51	28	
Pain, Muscle			
subjects affected / exposed	19 / 355 (5.35%)	21 / 362 (5.80%)	
occurrences (all)	54	78	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	86 / 355 (24.23%)	76 / 362 (20.99%)	
occurrences (all)	205	192	
Anorexia			
subjects affected / exposed	135 / 355 (38.03%)	153 / 362 (42.27%)	
occurrences (all)	383	479	
Constipation			
subjects affected / exposed	72 / 355 (20.28%)	46 / 362 (12.71%)	
occurrences (all)	145	77	
Dehydration			
subjects affected / exposed	8 / 355 (2.25%)	21 / 362 (5.80%)	
occurrences (all)	9	30	
Diarrhea			
subjects affected / exposed	211 / 355 (59.44%)	273 / 362 (75.41%)	
occurrences (all)	784	1079	

Flatulence			
subjects affected / exposed	19 / 355 (5.35%)	24 / 362 (6.63%)	
occurrences (all)	51	63	
Dry mouth			
subjects affected / exposed	24 / 355 (6.76%)	13 / 362 (3.59%)	
occurrences (all)	105	33	
Distension			
subjects affected / exposed	22 / 355 (6.20%)	26 / 362 (7.18%)	
occurrences (all)	61	98	
GI - Other			
subjects affected / exposed	29 / 355 (8.17%)	31 / 362 (8.56%)	
occurrences (all)	81	120	
Gastritis			
subjects affected / exposed	13 / 355 (3.66%)	24 / 362 (6.63%)	
occurrences (all)	32	53	
Heartburn			
subjects affected / exposed	21 / 355 (5.92%)	28 / 362 (7.73%)	
occurrences (all)	47	111	
Mucositis (functional/symptomatic), Oral cavity			
subjects affected / exposed	53 / 355 (14.93%)	72 / 362 (19.89%)	
occurrences (all)	134	176	
Nausea			
subjects affected / exposed	109 / 355 (30.70%)	90 / 362 (24.86%)	
occurrences (all)	259	212	
Taste Alteration			
subjects affected / exposed	10 / 355 (2.82%)	20 / 362 (5.52%)	
occurrences (all)	33	82	
Vomiting			
subjects affected / exposed	78 / 355 (21.97%)	82 / 362 (22.65%)	
occurrences (all)	150	140	
Hepatobiliary disorders			
Liver dysfunction			
subjects affected / exposed	21 / 355 (5.92%)	21 / 362 (5.80%)	
occurrences (all)	39	35	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	60 / 355 (16.90%)	41 / 362 (11.33%)	
occurrences (all)	111	138	
Dyspnea (shortness of breath)			
subjects affected / exposed	40 / 355 (11.27%)	35 / 362 (9.67%)	
occurrences (all)	74	79	
Pulmonary - Other			
subjects affected / exposed	20 / 355 (5.63%)	13 / 362 (3.59%)	
occurrences (all)	41	32	
Voice changes			
subjects affected / exposed	31 / 355 (8.73%)	31 / 362 (8.56%)	
occurrences (all)	116	120	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	13 / 355 (3.66%)	53 / 362 (14.64%)	
occurrences (all)	46	210	
Alopecia			
subjects affected / exposed	84 / 355 (23.66%)	46 / 362 (12.71%)	
occurrences (all)	352	222	
Dermatology - Other			
subjects affected / exposed	39 / 355 (10.99%)	55 / 362 (15.19%)	
occurrences (all)	142	184	
Rash/desquamation			
subjects affected / exposed	141 / 355 (39.72%)	186 / 362 (51.38%)	
occurrences (all)	536	785	
Pruritus			
subjects affected / exposed	44 / 355 (12.39%)	42 / 362 (11.60%)	
occurrences (all)	101	83	
Hand-foot skin reaction			
subjects affected / exposed	169 / 355 (47.61%)	136 / 362 (37.57%)	
occurrences (all)	805	723	
Dry skin			
subjects affected / exposed	33 / 355 (9.30%)	36 / 362 (9.94%)	
occurrences (all)	114	122	
Musculoskeletal and connective tissue disorders			

Musculoskeletal - Other subjects affected / exposed	28 / 355 (7.89%)	25 / 362 (6.91%)	

subjects affected / exposed	13 / 355 (3.66%)	20 / 362 (5.52%)	
occurrences (all)	24	57	
Hypophosphatemia			
subjects affected / exposed	38 / 355 (10.70%)	39 / 362 (10.77%)	
occurrences (all)	89	135	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2009	• Study design and plan: local ablation was deleted as a potentially curative intervention and transplant was added). • Exclusion criteria: Uncontrolled hypertension was defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg despite optimal medical management and clinically significant peripheral vascular disease was defined as symptomatic. • Removal of subjects from study • Administration of erlotinib and sorafenib was revised • Dose modification was revised • Permissible Concomitant Medications and Therapies were revised • Adverse Event Documentation was clarified for death and nonfatal serious adverse event (SAE) reporting • Detailed information for the genetic biomarker sampling were provided.
06 August 2010	• Revisions were made to relevant sections of the protocol to include South Africa in the stratification plan for randomization. • For HCC subjects without cirrhosis, the inclusion criterion was revised to add that the mandatory confirmation may also include cytological confirmation. • The use of the IWRS was added to all applicable sections. • Revisions were made to the section on the selection and timing of dose for each subject. • At 3 time points during the treatment period, the provisions under which additional cycles of therapy could be administered were revised to delete the requirements of ANC > 1000/µL and platelets > 50,000/µL. • Clarification was added to the prothrombin time for the calculation of the Child-Pugh score. • A note that strong inhibitors and inducers of CYP3A4 enzyme should be avoided during the study was added. • Statements were added to allow additional assessments to evaluate the status/activity of the hepatitis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported