Clinical trial results:
A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib

Summary

EudraCT number	2012-003649-14
Trial protocol	DE BE GB AT ES CZ FR HU NL IT
Global end of trial date	05 July 2019

Results information

Result version number	v2
This version publication date	15 July 2020
First version publication date	25 February 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/15982

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01774344
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate efficacy and safety of regorafenib in subjects with hepatocellular carcinoma (HCC) who had progressed after sorafenib.

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:

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

Evidence for comparator: -

Actual start date of recruitment	14 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	China: 137
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	France: 118
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 19

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	573
EEA total number of subjects	297

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)	315
From 65 to 84 years	258
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 14 May 2013 (first subject first visit) , 29 February 2016 (primary completion date)and 05-July-2019 (Last Patient Last Visit =End of study).

Pre-assignment

Screening details:

Overall, 843 subjects were screened, of them 270 subjects were screening failures. 573 subjects were randomized and assigned to treatment; of them 6 subjects never received treatment.436 Entered survival Follow-up and 4 End of survival follow-up data not available.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to regorafenib coated tablets orally every day for 3 weeks followed by 1 week off treatment plus best best supportive care.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to regorafenib coated tablets orally every day for 3 weeks followed by 1 week off treatment plus best BSC.

Arm title	Regorafenib 160 mg (BAY73-4506)

Arm description:

Subjects received regorafenib 160 milligram (mg) (4 * 40 mg coated tablets) orally every day for 3 weeks followed by 1 week off treatment plus BSC.

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

Dosage and administration details:

Subjects received regorafenib 160 mg coated tablets orally every day for 3 weeks followed by 1 week off treatment plus BSC.

Number of subjects in period 1	Placebo	Regorafenib 160 mg (BAY73-4506)
Started	194	379
Treated	193	374
Completed treatment	162	236
Entered survival FU	145	291
Not completed	194	379
Completed	0	0
Not completed	194	379
Consent withdrawn by subject	3	10
Death	132	253
Did not enter Survival Follow up	49	88
End of survival follow-up not available	2	2
Unspecified	-	1
Study Terminated by Sponsor	4	14
Lost to follow-up	4	10
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to regorafenib coated tablets orally every day for 3 weeks followed by 1 week off treatment plus best best supportive care.	
Reporting group title	Regorafenib 160 mg (BAY73-4506)
Reporting group description:	
Subjects received regorafenib 160 milligram (mg) (4 * 40 mg coated tablets) orally every day for 3 weeks followed by 1 week off treatment plus BSC.	

Reporting group values	Placebo	Regorafenib 160 mg (BAY73-4506)	Total
Number of subjects	194	379	573
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.1	61.8	
standard deviation	± 11.6	± 12.4	-
Gender categorical			
Units: Subjects			
Female	23	46	69
Male	171	333	504
Eastern cooperative oncology group (ECOG) Performance Status (PS) (data collection system-RAVE)			
ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours (h), 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair.			
Units: Subjects			
ECOG PS 0	130	247	377
ECOG PS 1	64	132	196
ECOG PS: Interactive voice response system (IVRS)			
ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 % waking h, 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair.			
Units: Subjects			
ECOG PS 0	129	251	380
ECOG PS 1	65	128	193
Alpha-fetoprotein (AFP) (RAVE)			
Alpha-Fetoprotein blood test was performed and baseline data were reported.			
Units: Subjects			
less than (<) 400 nanogram per milliliter (ng/mL)	107	217	324

greater than or equal to (>=) 400 ng/mL	87	162	249
Alpha-fetoprotein (AFP) (IVRS)			
AFP blood test was performed and baseline data were reported.			
Units: Subjects			
< 400 ng/mL	105	212	317
>= 400 ng/mL	89	167	256
Macrovascular invasion (RAVE)			
Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.			
Units: Subjects			
Absence	140	269	409
Presence	54	110	164
Macrovascular invasion (IVRS)			
Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.			
Units: Subjects			
Absence	135	262	397
Presence	59	117	176
The Barcelona-Clinic Liver Cancer (BCLC) stage at study entry			
BCLC classification divides HCC subjects in 5 stages (0=very early stage, A=early stage, B=intermediate stage, C=advanced stage and D=terminal stage) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Thus, it provides information on both prognostic prediction and treatment allocation.			
Units: Subjects			
Early stage	0	1	1
Intermediate stage	22	53	75
Advanced stage	172	325	497
Extrahepatic disease (RAVE)			
Extrahepatic disease defined as presence or absence of tumor outside the liver.			
Units: Subjects			
Absence	47	114	161
Presence	147	265	412
Extrahepatic disease (IVRS)			
Extrahepatic disease defined as presence or absence of tumor outside the liver.			
Units: Subjects			
Absence	62	129	191
Presence	132	250	382

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (N=573) included all randomized subjects.

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	573		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 61.6 ± 12.1		
Gender categorical Units: Subjects			
Female Male	69 504		
Eastern cooperative oncology group (ECOG) Performance Status (PS) (data collection system-RAVE)			
ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours (h), 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair.			
Units: Subjects			
ECOG PS 0 ECOG PS 1	377 196		
ECOG PS: Interactive voice response system (IVRS)			
ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 % waking h, 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair.			
Units: Subjects			
ECOG PS 0 ECOG PS 1	380 193		
Alpha-fetoprotein (AFP) (RAVE)			
Alpha-Fetoprotein blood test was performed and baseline data were reported.			
Units: Subjects			
less than (<) 400 nanogram per milliliter (ng/mL) greater than or equal to (>=) 400 ng/mL	324 249		
Alpha-fetoprotein (AFP) (IVRS)			
AFP blood test was performed and baseline data were reported.			
Units: Subjects			
< 400 ng/mL >= 400 ng/mL	317 256		
Macrovascular invasion (RAVE)			
Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.			
Units: Subjects			
Absence Presence	409 164		
Macrovascular invasion (IVRS)			
Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.			
Units: Subjects			
Absence Presence	262 117		
The Barcelona-Clinic Liver Cancer (BCLC) stage at study entry			

BCLC classification divides HCC subjects in 5 stages (0=very early stage, A=early stage, B=intermediate stage, C=advanced stage and D=terminal stage) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Thus, it provides information on both prognostic prediction and treatment allocation.			
Units: Subjects			
Early stage	1		
Intermediate stage	75		
Advanced stage	497		
Extrahepatic disease (RAVE)			
Extrahepatic disease defined as presence or absence of tumor outside the liver.			
Units: Subjects			
Absence	161		
Presence	412		
Extrahepatic disease (IVRS)			
Extrahepatic disease defined as presence or absence of tumor outside the liver.			
Units: Subjects			
Absence	191		
Presence	382		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to regorafenib coated tablets orally every day for 3 weeks followed by 1 week off treatment plus best best supportive care.	
Reporting group title	Regorafenib 160 mg (BAY73-4506)
Reporting group description:	
Subjects received regorafenib 160 milligram (mg) (4 * 40 mg coated tablets) orally every day for 3 weeks followed by 1 week off treatment plus BSC.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS (N=573) included all randomized subjects.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was defined as the time from date of randomization (Day 1) to death due to any cause. Subjects still alive at the time of analysis were censored at their last date of last contact.	
End point type	Primary
End point timeframe:	
From randomization (Day 1) of the first subject until 419 days later	

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: days				
median (confidence interval 95%)	237 (192 to 269)	323 (276 to 369)		

Statistical analyses

Statistical analysis title	Regorafenib v Placebo: Stratified (IVRS)
Statistical analysis description:	
Hazard ratio for OS and 95% confidence interval was calculated for stratified IVRS by using Cox model, stratified by the geographic region: Asia or Rest of the World (ROW), ECOG-PS: 0 versus 1, AFP level, presence versus absence of extrahepatic disease and presence versus absence of macrovascular invasion. Kaplan-Meier (KM) estimated for OS and KM survival curves were presented for each treatment arm.	
Comparison groups	Regorafenib 160 mg (BAY73-4506) v Placebo

Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000017
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.624
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.498
upper limit	0.782

Statistical analysis title	Regorafenib v Placebo: Stratified (RAVE)

Statistical analysis description:

Hazard ratio for OS and 95% confidence interval was calculated for stratified RAVE (Sensitivity) by using Cox model, stratified by the geographic region: Asia or Rest of the World (ROW), ECOG-PS: 0 versus 1, AFP level, presence versus absence of extrahepatic disease and presence versus absence of macrovascular invasion. Kaplan-Meier (KM) estimated for OS and KM survival curves were presented for each treatment arm.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000149
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.527
upper limit	0.828

Statistical analysis title	Regorafenib v Placebo: Unstratified (Sensitivity)

Statistical analysis description:

Hazard ratio for OS and 95% confidence interval was calculated for unstratified (sensitivity) by using Cox model, stratified by the geographic region: Asia or Rest of the World (ROW), ECOG-PS: 0 versus 1, AFP level, presence versus absence of extrahepatic disease and presence versus absence of macrovascular invasion. Kaplan-Meier (KM) estimated for OS and KM survival curves were presented for each treatment arm.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000107
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.674

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	0.831

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was the time (days) from randomization to radiological or clinical disease progression assessed by independent radiological review. Median and 95% confidence interval were reported for the modified response evaluation criteria in solid tumors (mRECIST) and response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) analysis sets. Subjects still alive at the time of analysis were censored at their last date of last contact.

End point type	Secondary

End point timeframe:

From date of randomization until 30 days after last study treatment (assessed every 6 weeks until PD; and after 8 cycle assessed every 12 weeks) (approximately 33 months)

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: days				
median (confidence interval 95%)				
mRECIST	45 (44 to 49)	97 (87 to 128)		
RECIST 1.1	45 (44 to 49)	119 (87 to 128)		

Statistical analyses

Statistical analysis title	Regorafenib v Placebo-mRECIST: Stratified (IVRS)

Statistical analysis description:

Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Kaplan-Meier estimates.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.439

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.355
upper limit	0.542

Statistical analysis title	Regorafenib v Placebo-mRECIST: Unstratified
Statistical analysis description:	
Hazard ratio and its 95% CI was based on unstratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Kaplan-Meier estimates.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.388
upper limit	0.572

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1:Stratified (IVRS)
Statistical analysis description:	
Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Kaplan-Meier estimates.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.334
upper limit	0.509

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1: Unstratified

Statistical analysis description:

Hazard ratio and its 95% CI was based on unstratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Kaplan-Meier estimates.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.365
upper limit	0.539

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival (PFS) was defined as the time (days) from date of randomization to date of disease progression (radiological or clinical) or death due to any cause, if death occurs before progression was documented. Death in the absence of progression was a PFS event only if it occurred within the 12+1 weeks for subjects who discontinued treatment prior to cycle 8 and 24+2 weeks for subjects who discontinued treatment after to cycle 8 of the last evaluable tumor assessment; PFS were censored at the date of the last evaluable tumor assessment, if it occurred later. Median and 95% confidence interval 95% were reported for the mRECIST and RECIST 1.1 analysis sets. Subjects still alive at the time of analysis were censored at their last date of last contact.

End point type	Secondary

End point timeframe:

From date of randomization until 30 days after last study treatment (assessed every 6 weeks until PD; and after 8 cycle assessed every 12 weeks)

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: days				
median (confidence interval 95%)				
mRECIST	45 (44 to 47)	95 (86 to 127)		
RECIST 1.1	45 (44 to 49)	102 (87 to 127)		

Statistical analyses

Statistical analysis title	Regorafenib v Placebo-mRECIST: Stratified (IVRS)
Statistical analysis description:	
Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Cox Regression Model.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.453
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.369
upper limit	0.555

Statistical analysis title	Regorafenib v Placebo-mRECIST: Unstratified
Statistical analysis description:	
Hazard ratio and its 95% CI was based on unstratified Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Cox Regression Model.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.397
upper limit	0.58

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1:Stratified (IVRS)
Statistical analysis description:	
Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Cox Regression Model.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)

Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.347
upper limit	0.522

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1: Unstratified

Statistical analysis description:

Hazard ratio and its 95% CI was based on unstratified Cox Regression Model. One-sided p-value was calculated from log rank test and 95% CIs was computed by using Cox Regression Model.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.454
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.376
upper limit	0.548

Secondary: Objective Tumor Response Rate (ORR)

End point title	Objective Tumor Response Rate (ORR)

End point description:

Objective tumor response rate (ORR) was defined as the percentage of subjects whose best tumor response CR or Partial Response (PR) observed during trial period assessed according to the mRECIST criteria and RECIST 1.1. CR= Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. PR= At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions. Subjects prematurely discontinuing without an assessment were to be considered non-responders for the analysis.

End point type	Secondary

End point timeframe:

From date of randomization until 30 days after last study treatment (assessed every 6 weeks until PD; and after 8 cycle assessed every 12 weeks) (approximately 33 months)

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: percentage of subjects				
number (not applicable)				
mRECIST	4.1	10.8		
RECIST 1.1	2.6	6.6		

Statistical analyses

Statistical analysis title	Regorafenib v Placebo-mRECIST
Statistical analysis description: Comparison of treatments were calculated.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00365
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-6.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.13
upper limit	-2.63

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1
Statistical analysis description: Comparison of treatments were calculated.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019991
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-4.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.55
upper limit	-0.75

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control rate (DCR) was defined as the percentage of subjects whose best response was CR (CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).), PR (PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.), or stable disease (SD) (SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.) according to RECIST and RECIST 1.1 criteria. SD had to be maintained for at least 6 weeks from the first demonstration of that rating.

End point type	Secondary

End point timeframe:

From date of randomization until 30 days after last study treatment (assessed every 6 weeks until PD; and after 8 cycle assessed every 12 weeks) (approximately 33 months)

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: percentage of subjects				
number (not applicable)				
mRECIST	36.1	65.2		
RECIST 1.1	34.5	65.7		

Statistical analyses

Statistical analysis title	Regorafenib v Placebo-mRECIST

Statistical analysis description:

Comparison of treatments were calculated.

Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-29.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.52
upper limit	-21.11

Statistical analysis title	Regorafenib v Placebo-RECIST 1.1
Statistical analysis description:	
Comparison of treatments were calculated.	
Comparison groups	Placebo v Regorafenib 160 mg (BAY73-4506)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-31.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.57
upper limit	-23.22

Other pre-specified: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was defined as the time from date of randomization (Day 1) to death due to any cause	
End point type	Other pre-specified
End point timeframe:	
From randomization (Day 1) of the first subject to end of follow upto 1710 days	

End point values	Placebo	Regorafenib 160 mg (BAY73-4506)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	379		
Units: days				
median (confidence interval 95%)	241 (196 to 274)	326 (278 to 372)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected after start of study drug administration until 30 days after end of study treatment over a period of approximately three years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Description: Subjects received placebo matched to regorafenib tablets orally every day for 3 weeks followed by 1 week off treatment plus best supportive care(BSC).

Reporting group title	Regorafenib (Stivarga, BAY73-4506)

Reporting group description:

Description: Subjects received regorafenib 160 mg (4 *40 mg tablets) orally every day for 3 weeks followed by 1 week off treatment plus BSC.

Serious adverse events	Placebo	Regorafenib (Stivarga, BAY73-4506)	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 193 (47.67%)	194 / 374 (51.87%)	
number of deaths (all causes)	176	324	
number of deaths resulting from adverse events	39	62	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine benign neoplasm			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 193 (0.00%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 193 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	1 / 2	
Orthostatic hypotension			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 193 (0.00%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Fatigue			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	25 / 193 (12.95%)	47 / 374 (12.57%)	
occurrences causally related to treatment / all	1 / 32	8 / 73	
deaths causally related to treatment / all	0 / 17	1 / 28	
Malaise			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	2 / 193 (1.04%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 193 (0.52%)	6 / 374 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Dyspnoea			
subjects affected / exposed	2 / 193 (1.04%)	5 / 374 (1.34%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Haemoptysis			
subjects affected / exposed	2 / 193 (1.04%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 193 (0.52%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	3 / 193 (1.55%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Tracheal disorder			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary venous thrombosis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 193 (1.04%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

General physical condition abnormal			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 193 (0.00%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial flutter			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute myocardial infarction			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	3 / 193 (1.55%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	3 / 193 (1.55%)	9 / 374 (2.41%)	
occurrences causally related to treatment / all	0 / 6	5 / 14	
deaths causally related to treatment / all	0 / 1	1 / 2	
Meningorrhagia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myasthenia gravis			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplegia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial venous sinus thrombosis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 193 (0.52%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 3	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal distension			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 193 (2.07%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	6 / 193 (3.11%)	10 / 374 (2.67%)	
occurrences causally related to treatment / all	0 / 7	1 / 13	
deaths causally related to treatment / all	0 / 1	0 / 2	
Constipation			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 193 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastritis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 193 (1.04%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	2 / 193 (1.04%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			

subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 193 (0.52%)	6 / 374 (1.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pancreatitis			
subjects affected / exposed	0 / 193 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 193 (1.55%)	6 / 374 (1.60%)	
occurrences causally related to treatment / all	0 / 5	3 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 193 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Bile duct stenosis			
subjects affected / exposed	2 / 193 (1.04%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	9 / 193 (4.66%)	9 / 374 (2.41%)	
occurrences causally related to treatment / all	5 / 14	1 / 14	
deaths causally related to treatment / all	2 / 5	0 / 3	
Hepatic function abnormal			
subjects affected / exposed	3 / 193 (1.55%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	2 / 193 (1.04%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 193 (0.52%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	2 / 193 (1.04%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 193 (0.52%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Precancerous skin lesion			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 193 (1.04%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Calculus urinary			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis noninfective			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
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	1 / 193 (0.52%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 193 (1.04%)	6 / 374 (1.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			

subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 193 (1.04%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	0 / 193 (0.00%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural infection bacterial			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 193 (0.52%)	8 / 374 (2.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 193 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	1 / 193 (0.52%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 193 (1.55%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 193 (0.00%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	2 / 193 (1.04%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 193 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 193 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Regorafenib (Stivarga, BAY73-4506)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 193 (83.94%)	366 / 374 (97.86%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 193 (7.25%)	119 / 374 (31.82%)	
occurrences (all)	30	327	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 193 (9.84%)	56 / 374 (14.97%)	
occurrences (all)	34	97	
Fatigue			
subjects affected / exposed	50 / 193 (25.91%)	110 / 374 (29.41%)	
occurrences (all)	67	205	
Malaise			
subjects affected / exposed	5 / 193 (2.59%)	23 / 374 (6.15%)	
occurrences (all)	5	33	
Oedema peripheral			
subjects affected / exposed	26 / 193 (13.47%)	63 / 374 (16.84%)	
occurrences (all)	32	81	
Pyrexia			
subjects affected / exposed	13 / 193 (6.74%)	79 / 374 (21.12%)	
occurrences (all)	15	113	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 193 (6.74%)	45 / 374 (12.03%)	
occurrences (all)	15	50	
Dyspnoea			
subjects affected / exposed	15 / 193 (7.77%)	26 / 374 (6.95%)	
occurrences (all)	15	42	
Dysphonia			
subjects affected / exposed	5 / 193 (2.59%)	68 / 374 (18.18%)	
occurrences (all)	7	85	
Pleural effusion			
subjects affected / exposed	10 / 193 (5.18%)	13 / 374 (3.48%)	
occurrences (all)	11	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 193 (4.15%)	30 / 374 (8.02%)	
occurrences (all)	8	35	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	21 / 193 (10.88%)	56 / 374 (14.97%)	
occurrences (all)	37	102	
Aspartate aminotransferase increased			
subjects affected / exposed	40 / 193 (20.73%)	99 / 374 (26.47%)	
occurrences (all)	89	234	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 193 (4.66%)	23 / 374 (6.15%)	
occurrences (all)	21	43	
Blood bilirubin increased			
subjects affected / exposed	30 / 193 (15.54%)	94 / 374 (25.13%)	
occurrences (all)	59	258	
Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 193 (7.25%)	24 / 374 (6.42%)	
occurrences (all)	32	73	
Lipase increased			
subjects affected / exposed	7 / 193 (3.63%)	27 / 374 (7.22%)	
occurrences (all)	15	62	
Platelet count decreased			
subjects affected / exposed	2 / 193 (1.04%)	39 / 374 (10.43%)	
occurrences (all)	8	129	
Weight decreased			
subjects affected / exposed	9 / 193 (4.66%)	55 / 374 (14.71%)	
occurrences (all)	11	132	
White blood cell count decreased			
subjects affected / exposed	2 / 193 (1.04%)	20 / 374 (5.35%)	
occurrences (all)	7	40	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 193 (6.22%)	25 / 374 (6.68%)	
occurrences (all)	12	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 193 (10.88%)	57 / 374 (15.24%)	
occurrences (all)	40	114	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	10 / 193 (5.18%)	20 / 374 (5.35%)	
occurrences (all)	13	24	
Abdominal pain upper			
subjects affected / exposed	18 / 193 (9.33%)	52 / 374 (13.90%)	
occurrences (all)	22	85	
Abdominal pain			
subjects affected / exposed	29 / 193 (15.03%)	85 / 374 (22.73%)	
occurrences (all)	43	127	
Ascites			
subjects affected / exposed	31 / 193 (16.06%)	61 / 374 (16.31%)	
occurrences (all)	57	91	
Constipation			
subjects affected / exposed	21 / 193 (10.88%)	67 / 374 (17.91%)	
occurrences (all)	24	79	
Diarrhoea			
subjects affected / exposed	31 / 193 (16.06%)	163 / 374 (43.58%)	
occurrences (all)	44	348	
Dry mouth			
subjects affected / exposed	12 / 193 (6.22%)	22 / 374 (5.88%)	
occurrences (all)	15	24	
Nausea			
subjects affected / exposed	26 / 193 (13.47%)	72 / 374 (19.25%)	
occurrences (all)	38	106	
Stomatitis			
subjects affected / exposed	4 / 193 (2.07%)	31 / 374 (8.29%)	
occurrences (all)	4	44	
Vomiting			
subjects affected / exposed	13 / 193 (6.74%)	50 / 374 (13.37%)	
occurrences (all)	17	73	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 193 (3.11%)	27 / 374 (7.22%)	
occurrences (all)	6	27	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	15 / 193 (7.77%)	194 / 374 (51.87%)	
occurrences (all)	27	554	
Pruritus			
subjects affected / exposed	14 / 193 (7.25%)	22 / 374 (5.88%)	
occurrences (all)	19	34	
Rash			
subjects affected / exposed	14 / 193 (7.25%)	21 / 374 (5.61%)	
occurrences (all)	15	28	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 193 (1.04%)	34 / 374 (9.09%)	
occurrences (all)	6	96	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 193 (0.52%)	29 / 374 (7.75%)	
occurrences (all)	1	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 193 (5.70%)	15 / 374 (4.01%)	
occurrences (all)	12	17	
Back pain			
subjects affected / exposed	16 / 193 (8.29%)	50 / 374 (13.37%)	
occurrences (all)	18	73	
Musculoskeletal pain			
subjects affected / exposed	11 / 193 (5.70%)	18 / 374 (4.81%)	
occurrences (all)	19	22	
Muscle spasms			
subjects affected / exposed	4 / 193 (2.07%)	38 / 374 (10.16%)	
occurrences (all)	5	48	
Pain in extremity			
subjects affected / exposed	5 / 193 (2.59%)	31 / 374 (8.29%)	
occurrences (all)	6	51	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 193 (15.03%)	122 / 374 (32.62%)	
occurrences (all)	37	186	

Hypoalbuminaemia			
subjects affected / exposed	14 / 193 (7.25%)	56 / 374 (14.97%)	
occurrences (all)	19	152	
Hypokalaemia			
subjects affected / exposed	6 / 193 (3.11%)	28 / 374 (7.49%)	
occurrences (all)	22	62	
Hyponatraemia			
subjects affected / exposed	7 / 193 (3.63%)	20 / 374 (5.35%)	
occurrences (all)	17	30	
Hypophosphataemia			
subjects affected / exposed	5 / 193 (2.59%)	36 / 374 (9.63%)	
occurrences (all)	11	96	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2013	-The term study drug treatment was substituted for regorafenib treatment in a sentence describing whether a subject could continue treatment if considered to be achieving a benefit from the treatment according to the investigator. - An inclusion criterion was modified according to the mRECIST and RECIST 1.1 in order to include subjects who demonstrated progression in previously treated lesions. - An exclusion criteria requiring the assessment of esophageal varices by endoscopy within 6 months and 12 months of the start of the study was modified to require that endoscopy be performed as per local standard of care. - In treatment assignment, text was modified stipulating that subjects should start treatment no later than 3 days after randomization. - Antiviral treatment for hepatitis C virus was included under "not permissible concomitant medication," in order to not include these subjects due to the unfavorable risk benefit assessment. - The measurement of vital signs was included separately from the physical examinations due to differences in the timing of those assessments. - Vital signs examinations were included to be carried out on Day 15 of each cycle consistent with the design of the electronic case report form (eCRF). - The section on Tumor response Criteria (RECIST 1.1 and mRECIST) was divided into subsections for clarity. Slight modifications were made to the introductory text for the RECIST 1.1 and the mRECIST criteria section for clarity.
13 December 2013	- Rewording was done for clarity regarding the planning of the formal futility and formal efficacy analyses stating that there would be one of type of analysis and that data reviews were to be performed according to the data monitoring committee (DMC) charter. - The text excluding subjects from the study who permanently discontinued sorafenib treatment due to any cause more than 8 weeks before randomization was changes to 10 weeks. This change was to allow additional time to recruit subjects who were transferred from other sites. - Under the subsection "Emergency unblinding by the investigator", text was added following ICH guidelines (ICH Topic E 6 [R1] Guideline for Good Clinical Practice) and in accordance with the Site User Manual for unblinding a subject's treatment assignment. - Text was added for clarification specifying exploratory pharmacokinetic (PK) analyses and an explanation of the timing of sample collection and the calculation of PK parameters. In addition a new subsection was added for completeness entitled "Validity of PK samples" describing the conditions under which PK samples were to be considered acceptable for analysis.
11 November 2014	- The number of subjects to be recruited into the study was increased from 530 to 560. - A change was introduced allowing the use of a separate non-genetic biomarker consent form in exceptional cases according to site-specific requirements. This change was introduced in order to cover the case where study sites required a separate non-genetic biomarker consent form. - Administrative changes
02 November 2015	-Changes regarding the planned interim analysis: The protocol requirement for performing a second interim efficacy analysis of the study results was removed. Due to the unexpectedly slow recruitment of subjects in China, the second interim analysis would have been conducted before full subject accrual into the study had been reached. It was considered important to optimize subject enrollment in China in light of a Health Authority guidance regarding enrollment. -Changes regarding monthly survival assessments: A requirement was added stating that monthly survival assessments were to continue until the approximate date of unblinding for primary completion of the study. If needed, survival assessments (for example via additional phone contacts) were to be allowed to continue past the primary analysis until the end of the study. This modification was included because overall survival data might be required after the primary completion of the study; additional analyses might be required to include the data from the data cut-off date (date at which approximately 370 events are achieved) up to or beyond the date of unblinding.

01 December 2015	-Information was added regarding interactions of regorafenib with neomycin, breast cancer resistant protein (BCRP), UGT1A1, UGT1A9, P-glycoprotein substrates, and bile saltsequestering agents. -The recommendation to proactively monitor subjects taking digoxin was removed. This information was added in light of new information that became available as documented in the latest version of the regorafenib IB. -References to Cytochrome P450 1A2 inhibitors and inducers were removed from the header and in the text since all of the substances were Cytochrome P450 3A4 (CYP 3A4) inhibitors. This change was introduced in order to clarify that only CYP 3A4 inhibitors and inducers. The underlining of the substances listed in the table was removed since there was no need to differentiate between these substances since all are either inhibitors or inducers of CYP34A.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Decimal places were automatically truncated if last decimal equals zero.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29704513

http://www.ncbi.nlm.nih.gov/pubmed/27932229