



Clinical trial results:

A Phase II uncontrolled study of BAY73-4506 in previously untreated patients with metastatic or unresectable renal cell cancer (RCC)

Summary

EudraCT number	2008-000107-28
Trial protocol	FI DE FR GB
Global end of trial date	02 April 2019

Results information

Result version number	v1 (current)
This version publication date	09 April 2020
First version publication date	09 April 2020

Trial information

Trial identification

Sponsor protocol code	11726/BAY73-4506
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00664326
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	24 April 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the antitumor activity and safety of BAY 73-4506 in previously untreated subjects with metastatic or unresectable RCC.

Secondary objectives included the evaluation of pharmacokinetic and biomarker data.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Finland: 10
Worldwide total number of subjects	49
EEA total number of subjects	47

Notes:

Subjects enrolled per age group

In utero	0
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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)	31
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male or female untreated participants, who were at least 18 years of age, with metastatic and/or unresectable, measurable predominantly clear cell renal cell cancer (RCC) histologically or cytologically documented could participate in this study at 18 centers in 6 countries.

Pre-assignment

Screening details:

Of 64 enrolled participants, 49 received study medication, and 15 were screen failures due to protocol violation (12 participants), withdrawal of consent (1 participant), adverse event (2 participants).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib (Stivarga, BAY73-4506)
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Arm description:

Participants received Regorafenib 160 mg per os (po) every day (qd) for 3 weeks on 1 week off of every 4 week cycle

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:

BAY 73-4506, 160 mg once daily for 3 weeks of every 4-week cycle (i.e., 3 weeks on, 1 week off)

Number of subjects in period 1	Regorafenib (Stivarga, BAY73-4506)
Started	49
Completed	1
Not completed	48
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Physician decision	1
Adverse event, non-fatal	14
Other Reasons	3
Disease Progression, Recurrence, or Relapse	24
Non-compliant with Study Medication	3

Baseline characteristics

Reporting groups

Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib 160 mg per os (po) every day (qd) for 3 weeks on 1 week off of every 4 week cycle	

Reporting group values	Regorafenib (Stivarga, BAY73-4506)	Total	
Number of subjects	49	49	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	18	18	
85 years and over	0	0	
Age Continuous			
Units: Years			
median	62.0		
full range (min-max)	40 to 76	-	
Sex: Female, Male			
Units:			
Female	22	22	
Male	27	27	
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
The ECOG PS ranged from Grades 0 to 5 (death). Grade 0 (fully active, able to carry on all pre-diseases performance without restriction) and Grade 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) were inclusion criteria.			
Units: Subjects			
PS 0	30	30	
PS 1	19	19	
Overall Motzer Score			
The Motzer score (high/poor risk, intermediate risk, low risk) is based on the number of the following poor prognostic features a participant possessed: ECOG >2, serum lactate dehydrogenase concentration > 1.5 times the upper limit of normal, hemoglobin < lower limit of normal, corrected calcium concentration > 10 mg/dl, and absence of prior nephrectomy. Participants who had none of these features = low risk; participants with 1 or 2 of these features = intermediate risk; participants with 3 or more of these features = high/poor risk and were excluded from participating in the study.			
Units: Subjects			
Low	24	24	
Intermediate	25	25	

End points

End points reporting groups

Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib 160 mg per os (po) every day (qd) for 3 weeks on 1 week off of every 4 week cycle	

Primary: Objective tumor response

End point title	Objective tumor response ^[1]
End point description:	
Objective tumor response of a participant was defined as the best tumor response (confirmed Complete Response [CR, tumor disappears] or Partial Response [PR, sum of lesion sizes decreased at least 30% from baseline]) observed during trial period assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) committee.	
End point type	Primary
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses of this primary endpoint is descriptive

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)	31.3			

Statistical analyses

No statistical analyses for this end point

Primary: Tumor response

End point title	Tumor response ^[2]
End point description:	
Tumor response of a participant was defined as the best tumor response (confirmed Complete Response [CR, tumor disappears], Partial Response [PR, sum of lesion sizes decreased at least 30% from baseline], Stable Disease [SD, steady state of disease], or Progressive Disease [PD, sum of lesion sizes increased at least 20% from smallest sum on study or new lesions]) observed during trial period assessed according to the RECIST committee.	
End point type	Primary
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses of this primary endpoint is descriptive.

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)				
Complete Response (CR)	0.0			
Partial Response (PR)	31.3			
Stable Disease (SD)	50.0			
Progressive Disease (PD)	10.4			
Not Assessable	8.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

End point title	Disease control
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End point description:

Disease control was defined as the percentage of participants who had a best response rating of CR (tumor disappears), PR (sum of lesion sizes decreased at least 30% from baseline), or SD (steady state of disease) that was maintained for at least 28 days from the first demonstration of that rating.

End point type	Secondary
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)	62.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall survival (OS) was calculated as the time from the first date of receiving study medication to death, due to any cause. Participants alive at the time of analysis were censored at their last date of follow-up.	
End point type	Secondary
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009).	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	99999 (285 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	
PFS was calculated as time from first date of receiving study drug until date of first observed disease progression (PD) (radiological or clinical, whichever was earlier) or death due to any cause, if death occurred before PD was documented. The actual date of tumor assessments (i.e., date on which radiological procedure was performed, rather than scheduled date) was used for this calculation to determine both the event date and censoring date. Patients without PD or death at time of analysis were censored at last date of tumor evaluation.	
End point type	Secondary
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	251 (160 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)
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End point description:

TTP was calculated as time from first date of receiving study drug until date of first documented disease progression (PD) (radiological or clinical, whichever was earlier). The actual date of tumor assessments (i.e., date on which radiological procedure was performed, rather than the scheduled date) was used for this calculation to determine both the event date and censoring date. Patients without PD at time of analysis were censored at last date of tumor evaluation.

End point type	Secondary
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	251 (167 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
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End point description:

Duration of response was defined as the time from the first documented objective response of PR or CR, whichever was earlier, to disease progression or death (if death occurred before progression was documented). Duration of response for subjects who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment.

End point type	Secondary
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Days				
median (confidence interval 95%)	99999 (140 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease (SD)

End point title	Duration of stable disease (SD)
End point description:	
Duration of SD was calculated as the time from the first date of receiving study drug until the date of documented PD or the last observation if the subject did not progress. Subjects without disease progression at the time of analysis were censored at the last date of tumor evaluation.	
End point type	Secondary
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 13 months later (13May2008 - 31May2009). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Days				
median (confidence interval 95%)	172 (107 to 99999)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective tumor response (Update)

End point title	Objective tumor response (Update)
End point description:	
Objective tumor response of a participant was defined as the best tumor response (confirmed Complete Response [CR, tumor disappears] or Partial Response [PR, sum of lesion sizes decreased at least 30% from baseline]) observed during trial period assessed according to the RECIST committee.	

End point type	Other pre-specified
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)	39.6			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tumor response (Update)

End point title	Tumor response (Update)
End point description:	
Tumor response of a participant was defined as the best tumor response (confirmed Complete Response [CR, tumor disappears], Partial Response [PR, sum of lesion sizes decreased at least 30% from baseline], Stable Disease [SD, steady state of disease], or Progressive Disease [PD, sum of lesion sizes increased at least 20% from smallest sum on study or new lesions]) observed during trial period assessed according to the RECIST committee.	
End point type	Other pre-specified
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)				
Complete Response (CR)	0.0			
Partial Response (PR)	39.6			
Stable Disease (SD)	41.7			
Progressive Disease (PD)	10.4			
Not Assessable	8.3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disease control (Update)

End point title	Disease control (Update)
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End point description:

Disease control was defined as the percentage of participants who had a best response rating of CR (tumor disappears), PR (sum of lesion sizes decreased at least 30% from baseline), or SD (steady state of disease) that was maintained for at least 28 days from the first demonstration of that rating.

End point type	Other pre-specified
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of participants				
number (not applicable)	62.5			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival (Update)

End point title	Overall survival (Update)
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End point description:

Overall survival (OS) was calculated as the time from the first date of receiving study medication to death, due to any cause. Participants alive at the time of analysis were censored at their last date of follow-up.

End point type	Other pre-specified
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011).

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	99999 (735 to 99999)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival (Update)

End point title	Progression-free survival (Update)
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End point description:

PFS was calculated as time from first date of receiving study drug until date of first observed disease progression (PD) (radiological or clinical, whichever was earlier) or death due to any cause, if death occurred before PD was documented. The actual date of tumor assessments (i.e., date on which radiological procedure was performed, rather than scheduled date) was used for this calculation to determine both the event date and censoring date. Patients without PD or death at time of analysis were censored at last date of tumor evaluation.

End point type	Other pre-specified
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	335 (167 to 438)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to progression (Update)

End point title	Time to progression (Update)
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End point description:

TTP was calculated as time from first date of receiving study drug until date of first documented disease progression (PD) (radiological or clinical, whichever was earlier). The actual date of tumor assessments (i.e., date on which radiological procedure was performed, rather than the scheduled date) was used for this calculation to determine both the event date and censoring date. Patients without PD at time of analysis were censored at last date of tumor evaluation.

End point type	Other pre-specified
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End point timeframe:

From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
median (confidence interval 95%)	335 (167 to 454)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of response (Update)

End point title	Duration of response (Update)
End point description:	
Duration of response was defined as the time from the first documented objective response of PR or CR, whichever was earlier, to disease progression or death (if death occurred before progression was documented). Duration of response for subjects who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment.	
End point type	Other pre-specified
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Days				
median (confidence interval 95%)	428 (250 to 540)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of stable disease (Update)

End point title	Duration of stable disease (Update)
End point description:	
Duration of SD was calculated as the time from the first date of receiving study drug until the date of documented PD or the last observation if the subject did not progress. Subjects without disease progression at the time of analysis were censored at the last date of tumor evaluation.	

End point type	Other pre-specified
End point timeframe:	
From start of treatment of the first participant until database cut-off approximately 37 months later (13May2008 - 1Jun2011). Assessed every 8 weeks for 6 months, then every 12 weeks	

End point values	Regorafenib (Stivarga, BAY73-4506)			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Days				
median (confidence interval 95%)	119 (105 to 335)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment up to 30 days after the last dose of study drug

Adverse event reporting additional description:

Acronyms used in Adverse events section: Gastrointestinal (GI), Not Otherwise Specified (NOS), Absolute Neutrophil Count (ANC), Common Terminology Criteria for Adverse Events (CTCAE).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Regorafenib (BAY73-4506)
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Reporting group description:

Subjects received regorafenib 160 mg po qd for 3 weeks of every 4 week cycle (3 weeks on, 1 week off).

Serious adverse events	Regorafenib (BAY73-4506)		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 49 (65.31%)		
number of deaths (all causes)	39		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian adenoma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tumour excision			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Laryngospasm			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Myocardial infarction			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct obstruction			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Regorafenib (BAY73-4506)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 49 (97.96%)		
Investigations			
Amylase increased			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	12		
Blood creatinine increased			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	7		
Lipase increased			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	29		
Weight decreased			

subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	86		
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 49 (51.02%)		
occurrences (all)	338		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	7		
Ageusia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	14 / 49 (28.57%)		
occurrences (all)	47		
Neuropathy peripheral			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	8		
Paraesthesia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	61		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	22 / 49 (44.90%)		
occurrences (all)	192		
Chest pain			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	19		
Chills			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	6		
Oedema peripheral			

subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	13		
Mucosal inflammation			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	11		
Pain			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	31		
Pyrexia			
subjects affected / exposed	9 / 49 (18.37%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	11		
Anaemia			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	9		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 49 (34.69%)		
occurrences (all)	112		
Dysphagia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	16 / 49 (32.65%)		
occurrences (all)	46		
Vomiting			
subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	29		
Abdominal pain			
subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	37		
Abdominal pain upper			

subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	28		
Diarrhoea			
subjects affected / exposed	24 / 49 (48.98%)		
occurrences (all)	215		
Dyspepsia			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	7		
Glossodynia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Oral pain			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	35		
Stomatitis			
subjects affected / exposed	15 / 49 (30.61%)		
occurrences (all)	108		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	15		
Dysphonia			
subjects affected / exposed	18 / 49 (36.73%)		
occurrences (all)	50		
Dyspnoea			
subjects affected / exposed	16 / 49 (32.65%)		
occurrences (all)	48		
Epistaxis			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Palmar erythema subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash generalised subjects affected / exposed occurrences (all)	22 / 49 (44.90%) 139		
	5 / 49 (10.20%) 16		
	6 / 49 (12.24%) 77		
	5 / 49 (10.20%) 19		
	4 / 49 (8.16%) 8		
	3 / 49 (6.12%) 3		
	34 / 49 (69.39%) 402		
	17 / 49 (34.69%) 74		
	3 / 49 (6.12%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 23		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	7 / 49 (14.29%) 120		

subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	55		
Bone pain			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	25		
Muscle spasms			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	53		
Musculoskeletal pain			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	23		
Neck pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	12		
Pain in extremity			
subjects affected / exposed	11 / 49 (22.45%)		
occurrences (all)	85		
Infections and infestations			
Rhinitis			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	6		
Infection			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	9 / 49 (18.37%)		
occurrences (all)	21		
Oral candidiasis			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	6		

Urinary tract infection subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 13		
Metabolism and nutrition disorders			
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 13		
Decreased appetite subjects affected / exposed occurrences (all)	16 / 49 (32.65%) 104		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2008	A Data Monitoring Committee was added. Clarification was provided for how the risk/benefit was to be assessed during the study and how the termination/continuation would be evaluated. The frequency of tumor assessments after month 6 (cycle 6) was decreased from every 8 weeks to every 12 weeks. The timing of disease assessments was clarified. The packaging configuration for study medication was added. Assessments (tissue and blood biomarker samples, vital signs, blood pressure, and laboratory evaluations) were clarified. The description of Adverse Events handling was updated to reflect Bayer oncology standards. Pharmacokinetic Sample Handling Instructions were removed to avoid duplication of instructions that were already present in a separate Laboratory Manual.
19 August 2008	Subjects who remained on treatment following disease progression were no longer required to undergo radiological evaluations for the purpose of tumor response assessment. Describe changes to the 20mg tablet formulation and add the 40mg tablet formulation. Background safety data was updated.
30 January 2009	Subjects who had disease progression while receiving study drug were allowed to remain on treatment if the investigator and sponsor felt that the subject would benefit.
05 June 2009	Subjects were required to undergo a full urinalysis, rather than dipstick. Additionally, the frequency of urinalysis, chemistry, and electrolyte panels was increased to every 2 weeks instead of at the beginning of each 4-week cycle.
02 December 2010	Clarified that Day 15 laboratory assessments were not required after 6 cycles of treatment if the subject continued to receive clinical benefit from treatment and there were no clinically significant laboratory abnormalities.
15 July 2011	The purpose of Amendment 6, a global amendment, was to increase liver function test monitoring and include a dose modification table for AST, ALT and bilirubin in the protocol.
04 December 2012	The purpose of Amendment 7, a global amendment, was to allow for less frequent imaging procedures and laboratory assessment for patients who have been on treatment for more than 2 years (24 cycles).

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.

"99999" entered in the form stands for "Not Applicable".

Notes: