Clinical trial results:
A prospective, single-arm, multicenter, uncontrolled, open-label Phase II trial of refametinib (BAY 86-9766) in patients with RAS mutant Hepatocellular Carcinoma (HCC)

Summary

EudraCT number	2013-000311-25
Trial protocol	CZ BE AT GB DE HU ES IT FR
Global end of trial date	08 October 2014

Results information

Result version number	v2 (current)
This version publication date	07 September 2016
First version publication date	13 July 2016
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-9766/16553

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01915589
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	08 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of refametinib in subjects with GTPase KRas (Kirsten rat sarcoma viral oncogene homolog) (KRAS) or Neuroblastoma RAS viral oncogene homolog (NRAS) mutant unresectable or metastatic Hepatocellular Carcinoma (HCC).

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	16 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	16
EEA total number of subjects	8

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)	6
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 58 study centers in 17 countries, from 16 September 2013 (first subject first visit) to 08 October 2014 (last subject last visit).

Pre-assignment

Screening details:

Overall 498 subjects were included in screening phase 1 (RAS mutation test), of which 25 were completed phase 1 and were enrolled in screening phase 2; resulting in a total of 16 subjects who assigned to treatment.

Period 1

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

Arms

Arm title	Refametinib (BAY86-9766)

Arm description:

Subjects received refametinib (BAY86-9766) tablets at a dose of 50 milligram (mg) orally, twice daily (12 hours apart) in each treatment cycle until disease progression (defined by modified response evaluation criteria in solid tumors [mRECIST]=at least a 20 percent [%] increase in the sum of diameters of target lesions, taking the smallest sum on study as reference), clinical progression (example: eastern cooperative oncology group performance status [ECOG PS] of at least 3), or another criterion for discontinuation of treatment was reached. A treatment cycle consisted of 21 days.

Arm type	Experimental
Investigational medicinal product name	Refametinib
Investigational medicinal product code	BAY86-9766
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received refametinib 50 mg (1x20 mg + 1x30 mg or 50 mg tablet) twice daily (bid).

Number of subjects in period 1	Refametinib (BAY86-9766)
Started	16
Safety follow-up performed	14
Safety follow-up completed	10
Entered survival follow-up	11
Discontinued survival follow-up	11
Completed	0
Not completed	16
Death	2
Progressive disease (PD) - Clinical	2
AE associated with clinical PD	2

Non-compliance with study drug	1
Adverse event (AE) not associated with clinical PD	2
PD - Radiological	3
Consent withdrawn by subject	4

Baseline characteristics

Reporting groups	
Reporting group title	Refametinib (BAY86-9766)

Reporting group description:

Subjects received refametinib (BAY86-9766) tablets at a dose of 50 milligram (mg) orally, twice daily (12 hours apart) in each treatment cycle until disease progression (defined by modified response evaluation criteria in solid tumors [mRECIST]=at least a 20 percent [%] increase in the sum of diameters of target lesions, taking the smallest sum on study as reference), clinical progression (example: eastern cooperative oncology group performance status [ECOG PS] of at least 3), or another criterion for discontinuation of treatment was reached. A treatment cycle consisted of 21 days.

Reporting group values	Refametinib (BAY86-9766)	Total	
Number of subjects	16	16	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 65.8 ± 12.3	 -	
Gender Categorical Units: Subjects			
Female	3	3	
Male	13	13	
Race Units: Subjects			
White	9	9	
Asian	7	7	
Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease 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, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death.			
Units: Subjects			
Fully Active	7	7	
Restricted Active	9	9	
Barcelona Clinic Liver Cancer (BCLC) stage			
Barcelona Clinic Liver Cancer (BCLC)			
Units: Subjects			
B (Intermediate Stage)	2	2	
C (Avanced Stage)	14	14	
Child Pugh Classification A Units: Subjects			
Child Pugh Classification A	16	16	

End points

End points reporting groups

Reporting group title	Refametinib (BAY86-9766)

Reporting group description:

Subjects received refametinib (BAY86-9766) tablets at a dose of 50 milligram (mg) orally, twice daily (12 hours apart) in each treatment cycle until disease progression (defined by modified response evaluation criteria in solid tumors [mRECIST]=at least a 20 percent [%] increase in the sum of diameters of target lesions, taking the smallest sum on study as reference), clinical progression (example: eastern cooperative oncology group performance status [ECOG PS] of at least 3), or another criterion for discontinuation of treatment was reached. A treatment cycle consisted of 21 days.

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

Subject analysis set description:

FAS (N=16) included all subjects who were assigned to study treatment.

Primary: Objective Response Rate (ORR) According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Assessed by Central Radiological Review

End point title	Objective Response Rate (ORR) According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Assessed by Central Radiological Review[1]

End point description:

ORR was defined as the proportion of subjects with the best tumor response (confirmed completeresponse [CR] or partial response [PR]) achieved over the whole duration of study as per the mRECIST. CR=disappearance of all target lesions, and PR=at least a 30% decrease in the sum of diameters of target lesions taking the baseline sum of diameters as the reference.ORR=CR+PR. CR and PR were confirmed by a second assessment at least four weeks later.

End point type	Primary

End point timeframe:

From study treatment until approximately 1 year later, assessed every 6 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: Descriptive statistics were planned to report, Inferential statistics were not analysed for this endpoint.

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[2]			
Units: percentage of subjects				
number (confidence interval 95%)				
Responders	0 (0 to 0)			
Non-responders	100 (79.41 to 100)			

Notes:

[2] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Assessed by Central Radiological Review

End point title	Objective Response Rate (ORR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Assessed by Central Radiological Review

End point description:

ORR was defined as the proportion of subjects with the best tumor response (confirmed CR or PR) achieved over the whole duration of study as per the RECIST version 1.1. CR=disappearance of all target lesions, and PR=at least a 30% decrease in the sum of diameters of target lesions taking the baseline sum of diameters as the reference. ORR=CR+PR. CR and PR were confirmed by a second assessment at least four weeks later.

End point type	Secondary

End point timeframe:

From study treatment until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[3]			
Units: percentage of subjects				
number (confidence interval 95%)				
Responders	0 (0 to 0)			
Non-responders	100 (79.41 to 100)			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) Assessed by Investigator

End point title	Objective Response Rate (ORR) Assessed by Investigator

End point description:

ORR was defined as the proportion of subjects with the best tumor response (confirmed CR or PR) achieved over the whole duration of study as per the mRECIST and RECIST version 1.1 using investigator assessment. CR=disappearance of all target lesions, and PR=at least a 30% decrease in the sum of diameters of target lesions taking the baseline sum of diameters as the reference. ORR=CR+PR. CR and PR were confirmed by a second assessment at least four weeks later.

End point type	Secondary

End point timeframe:

From study treatment until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[4]			
Units: percentage of subjects				
number (confidence interval 95%)				
mRECIST: Responders	0 (0 to 0)			
mRECIST: Non-responders	100 (79.41 to 100)			

RECIST: Responders	0 (0 to 0)			
RECIST: Non-responders	100 (79.41 to 100)			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Assessed by Central Radiological Review (CRR) and Investigator

End point title	Disease Control Rate (DCR) Assessed by Central Radiological Review (CRR) and Investigator

End point description:

Disease control rate (DCR) was defined as the proportion of subjects who had a best radiological response rating over the whole duration of the study of CR, PR, or stable disease (SD).

End point type	Secondary

End point timeframe:

From study treatment until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[5]			
Units: percentage of subjects				
number (confidence interval 95%)				
CRR: mRECIST-Responder	56.3 (29.88 to 80.25)			
CRR: mRECIST-Non-Responder	43.8 (19.75 to 70.12)			
Investigator: mRECIST-Responder	56.3 (29.88 to 80.25)			
Investigator: mRECIST-Non-Responder	43.8 (19.75 to 70.12)			
CRR: RECIST-Responder	62.5 (35.43 to 84.8)			
CRR: RECIST-Non-Responder	37.5 (15.2 to 64.57)			
Investigator: RECIST-Responder	62.5 (35.43 to 84.8)			
Investigator: RECIST-Non-Responder	37.5 (15.2 to 64.57)			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was defined as the time from the first day with study drug intake (dose greater than zero) until death from any cause or until the last date the subject was known to be alive. 99999 indicates that the data cannot be estimated due to censored data.

End point type	Secondary

End point timeframe:

From start of treatment of the first subject until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Days				
median (confidence interval 95%)	177 (58 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Radiographic Tumor Progression (TTP) Assessed by Central Radiological Review and Investigator

End point title	Time to Radiographic Tumor Progression (TTP) Assessed by Central Radiological Review and Investigator

End point description:

Time to radiographic tumor progression (TTP) was defined as the time from the date of the first dose of study treatment to the date of the first observed radiographically documented disease progression. The actual date of tumor assessment was used for this calculation. 99999 indicates that the data cannot be estimated due to censored data.

End point type	Secondary

End point timeframe:

From start of treatment of the first subject until approximately 1 year, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[6]			
Units: Days				
median (confidence interval 95%)				
CRR- mRECIST	84 (42 to 99999)			
CRR- RECIST	84 (42 to 99999)			
Investigator- mRECIST	84 (42 to 99999)			
Investigator- RECIST	84 (42 to 99999)			

Notes:
[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Response Assessed by Central Radiological Review and Investigator

End point title	Tumor Response Assessed by Central Radiological Review and Investigator

End point description:

Tumor response (Best overall response [BOR]) was defined as the best tumor response CR, PR, SD, or PD observed during trial period assessed according to the mRECIST and RECIST V 1.1 criteria. CR was defined as disappearance of tumor lesions, PR was defined as a decrease of at least 30% in the sum of tumor lesion sizes, SD was defined as steady state of disease, PD was defined as an increase of at least 20% in the sum of tumor lesions sizes.

End point type	Secondary

End point timeframe:

From start of treatment of the first subject until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[7]			
Units: percentage of subjects				
number (confidence interval 95%)				
CRR- mRECIST: Unconfirmed PR	6.3 (0.16 to 30.23)			
CRR- mRECIST: SD	50 (24.65 to 75.35)			
CRR- mRECIST: PD	18.8 (4.05 to 45.65)			
CRR- mRECIST: Missing	25 (7.27 to 52.38)			
Investigator - mRECIST: SD	56.3 (29.88 to 80.25)			
Investigator - mRECIST: PD	18.8 (4.05 to 45.65)			
Investigator - mRECIST: Missing	25 (7.27 to 52.38)			
CRR - RECIST: SD	62.5 (35.43 to 84.8)			
CRR - RECIST: PD	12.5 (1.55 to 38.35)			
CRR - RECIST: Missing	25 (7.27 to 52.38)			
Investigator - RECIST: SD	62.5 (35.43 to 84.8)			
Investigator - RECIST: PD	12.5 (1.55 to 38.35)			

Investigator - RECIST: Missing	25 (7.27 to 52.38)			

Notes:

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Assessed by Central Radiological Review and Investigator

End point title	Progression-free Survival (PFS) Assessed by Central Radiological Review and Investigator

End point description:

PFS was defined as the time from date of starting treatment to disease progression, radiological or clinical, or death due to any cause, whichever occurs first. Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation.

End point type	Secondary

End point timeframe:

From start of treatment of the first subject until approximately 1 later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[8]			
Units: Days				
median (confidence interval 95%)				
CRR- mRECIST	58 (42 to 133)			
CRR- RECIST	58 (42 to 133)			
Investigator- mRECIST	58 (32 to 124)			
Investigator- RECIST	82 (32 to 124)			

Notes:

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. TEAE was defined as any AE arising or worsening after the first dose of study treatment and not later than 30 days after the last study drug intake. Safety analysis set (SAF) included all subjects in FAS with atleast one intake of the study drug.

End point type	Secondary

End point timeframe:

Start of study drug administration until 30 days after the last dose of study drug intake (approximately 1 year)

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	16[9]			
Units: subjects	16			

Notes:

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response was defined as the time from date of first objective radiological response CR or PR to the date when PD was first documented radiologically or death (if death occurred first) according to mRECIST. DOR was evaluated only for subjects who achieved their confirmed best response as CR or PR. Subjects still having CR or PR and have not died at the time of analysis were censored at their last date of tumor evaluation. Duration of response defined for responders only (that is CR or PR).

End point type	Secondary

End point timeframe:

From study treatment until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: days				

Notes:

[10] - No objective responses were observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response

End point title	Time to Objective Response

End point description:

Time to Objective Response for subjects who achieved an objective response (Complete Response (CR) or Partial Response (PR)) was defined as the time from date of starting treatment to the earliest date that the objective response was first documented according to mRECIST.

End point type	Secondary

End point timeframe:

From start of treatment of the first subject until approximately 1 year later, assessed every 6 weeks

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: days				

Notes:

[11] - No objective responses were observed.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Reported Outcomes (PRO)

End point title	Patient Reported Outcomes (PRO)

End point description:

PRO was planned to be analysed during Stage 2 of the study using psychometrically sound questionnaire which was developed to measure quality of life in subjects with hepatobiliary cancers.

End point type	Other pre-specified

End point timeframe:

Day 1 of each cycle, end of treatment during Stage II of the study

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: subjects				

Notes:

[12] - As the study did not continue to Stage 2 there were no subject reported outcome analyses.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic Analysis

End point title	Pharmacokinetic Analysis

End point description:

Plasma concentrations of refametinib and metabolites (BAY 1085159 [metabolite M-17] and BAY 1045650 [metabolite M-11]) were evaluated. 3 samples collected on Cycle 1, Day 15.

End point type	Other pre-specified

End point timeframe:

Cycle 1, Day 15

End point values	Refametinib (BAY86-9766)			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: subjects				

Notes:

[13] - Data were planned not to be summarized in the report.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of study drug administration until 30 days after the last dose of study drug intake, (approximately 1 year)

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Refametinib (BAY86-9766), 50 mg twice daily, Phase II

Reporting group description:

Subjects received refametinib (BAY86-9766) tablets at a dose of 50 mg orally, twice daily (12 hours apart) in each treatment cycle until disease progression (defined by mRECIST= at least a 20% increase in the sum of diameters of target lesions, taking the smallest sum on study as reference) assessed by central image review, clinical progression (example: ECOG PS of at least 3), or another criterion for discontinuation of treatment was reached. A treatment cycle consisted of 21 days.

Serious adverse events	Refametinib (BAY86-9766), 50 mg twice daily, Phase II		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death NOS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Multi-organ failure			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
CPK increased			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heart failure			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Transient ischemic attacks			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal hemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders - Other, specify			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations - Other, specify			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 16 (6.25%)		
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	Refametinib (BAY86-9766), 50 mg twice daily, Phase II		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
General disorders and administration site conditions			

Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Malaise subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Localized edema subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Edema limbs subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 8		
Fever subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Fatigue subjects affected / exposed occurrences (all)	6 / 16 (37.50%) 13		
Edema trunk subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Flu like symptoms subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 3		
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Genital edema subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Respiratory, thoracic and mediastinal disorders			

Sore throat			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dyspnea			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Personality change			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hallucinations			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
Weight loss			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
White blood cell decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Serum amylase increased			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
Platelet count decreased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	6		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Creatinine increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
CPK increased			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Investigations - Other, specify			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 7		
Somnolence subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Neuralgia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Encephalopathy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 3		
Syncope subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Blurred vision subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	5 / 16 (31.25%) 6		
Duodenal ulcer subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Constipation subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Abdominal pain			

subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
Ascites				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
Vomiting				
subjects affected / exposed	6 / 16 (37.50%)			
occurrences (all)	10			
Gastrointestinal disorders - Other, specify				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	4			
Oral hemorrhage				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	6 / 16 (37.50%)			
occurrences (all)	8			
Dyspepsia				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Hemorrhoidal hemorrhage				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Gastric hemorrhage				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Esophageal ulcer				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Mucositis oral				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	4			

Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Rash acneiform			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	8		
Pruritus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Erythema multiforme			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	11		
Skin ulceration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Acute kidney injury			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Generalized muscle weakness			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Peritoneal infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Enterocolitis infectious			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Metabolism and nutrition disorders - Other, specify			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Hyperuricemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hyperglycemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Hyponatremia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Hypoglycemia			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Hypoalbuminemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
Dehydration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2013	Wording regarding use of refametinib tablets was clarified. Based on final pharmacokinetic results from a clinical relative bioavailability study (15221), tablets exhibit comparable bioavailability to capsules. Therefore tablets could be used as an alternative for capsules. It was also indicated that tablets may be taken with or without a meal. - An inconsistency was corrected; word "sorafenib" was removed from sub-heading as text described a study where only refametinib was used. -Contact information for study medical expert was updated. - Prior cytotoxic chemotherapy was not allowed according to Amendment 1. The removal of prior cytotoxic chemotherapy was deemed necessary to exclude a population of overtreated subjects who may have been potentially different from the subjects conventionally treated with sorafenib. This change affected eligibility criterion for RAS mutation testing and exclusion criteria (excluded previous therapies and medications). -Exclusion criterion regarding hepatitis B infection was amended; an incorrect footnote was removed. -Exclusion criterion regarding women of childbearing potential was amended to reduce the time gap between the pregnancy evaluation and the beginning of treatment. - Guidance regarding reporting of contrast media was added. -In order to characterize the cardiovascular safety at anticipated maximum plasma concentrations of the study treatment, additional safety electrocardiogram (ECGs) were added. -A footnote regarding the documentation of the previous therapy for HCC was amended to correct inconsistency. Wording regarding documentation of the baseline subject data pertaining to demographic information was corrected. -Reference for important medical events was updated. -Two paragraphs regarding the documentation of AEs were combined to improve clarity of the text. -Wording regarding the missing PRO assessments was corrected.

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.

The study did not proceed to Stage 2 due to failure in achieving ORR by at least 5 of the first 15 treated subjects in Stage 1, as planned. 99999 = data was not available or estimable. Bio-marker analysis will be reported retrospectively.

Notes: