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

Summary

EudraCT number	2013-000241-39
Trial protocol	AT CZ GB DE BE IT HU ES
Global end of trial date	08 February 2017

Results information

Result version number	v1 (current)
This version publication date	10 February 2018
First version publication date	10 February 2018

Trial information

Trial identification

Sponsor protocol code	BAY86-9766 / 16728

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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-trialscontact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trialscontact@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 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2017
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 combination with sorafenib in subjects with Kirsten rat sarcoma viral oncogene homolog (KRAS/GTPase 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 Council of 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	27 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	19 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Thailand: 1
Worldwide total number of subjects	16
EEA total number of subjects	9

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)	8
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study conducted in 21 countries (Austria, Belgium, China, Czech Republic, France, Germany, United Kingdom, Hong Kong, Hungary, Israel, Italy, Japan, New Zealand, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United States) between 27 September 2013 (first subject first visit) and 08 February 2017 (last subject last visit).

Pre-assignment

Screening details:

In Stage 1 of the study, 820 subjects were included in screening phase 1 for KRAS or NRAS mutations, of them 24 completed screening phase 1 and enrolled for screening phase 2 (for study treatment eligibility). In phase 2 screening, 7 were screening failures and 1 died. Finally, 16 subjects were assigned to treatment. Stage 2 was not performed.

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 50 mg BID + Sorafenib 400 mg BID

Arm description:

Subjects received refametinib 50 milligram (mg) as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally, twice daily (bid) in combination with sorafenib 400 mg as tablets (2 * 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no hand-foot skin reaction (HFSR), fatigue, or gastrointestinal (GI) toxicities of grade 2 or higher occurred.

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

Dosage and administration details:

Subjects received sorafenib 400 mg as tablets (2 * 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

Investigational medicinal product name	Refametinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received refametinib 50 mg as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally bid, without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met.

Number of subjects in period 1	Refametinib 50 mg BID + Sorafenib 400 mg BID
Started	16
Completed	12
Not completed	4
Consent withdrawn by subject	2
AE Not Associated With ClinicalDisease Progression	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	16	16	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	67.2		
standard deviation	± 8.3	-	
Gender Categorical Units: Subjects			
Female	4	4	
Male	12	12	
Eastern cooperative oncology group (ECOG) Performance Status (PS)			
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			
Fully Active	10	10	
Restricted Active	6	6	
Macrovascular Invasion			
Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.			
Units: Subjects			
No	9	9	
Yes	7	7	
Barcelona Clinic Liver Cancer (BCLC) stage			
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 providesinformation on both prognostic prediction and treatment allocation.			
Units: Subjects			
A (Early Stage)	2	2	
B (Intermediate Stage)	2	2	
C (Advanced Stage)	12	12	

End points

End points reporting groups

Reporting group title	Refametinib 50 mg BID + Sorafenib 400 mg BID

Reporting group description:

Subjects received refametinib 50 milligram (mg) as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally, twice daily (bid) in combination with sorafenib 400 mg as tablets (2 * 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no hand-foot skin reaction (HFSR), fatigue, or gastrointestinal (GI) toxicities of grade 2 or higher occurred.

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

Subject analysis set description:

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

Subject analysis set title	Asia population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asia population (N=6) included all Asian subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

Subject analysis set title	RoW population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

RoW population (N=10) included all RoW subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

Primary: Objective Tumor Response Rate (ORR) According to mRECIST Assessed by Central Radiological Review

End point title	Objective Tumor Response Rate (ORR) According to mRECIST Assessed by Central Radiological Review[1]

End point description:

ORR was defined as the proportion of subjects who had a best response rating over the whole duration of the study of complete response (CR) or partial response (PR) according to mRECIST. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of less than (<) 10 millimeter (mm). PR was defined as at least a 30 percent (%) decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

End point type	Primary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

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: As Stage 1 of the study was exploratory, there was no statistical testing at the end of Stage 1; all analyses were descriptive only.

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[2]	10[3]		
Units: Subjects				
Responder	0	0		
Non-Responder	6	10		

Notes:

[2] - FAS

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: ORR According to RECIST v.1.1 Assessed by Central Radiological Review

End point title	ORR According to RECIST v.1.1 Assessed by Central Radiological Review

End point description:

ORR was defined as the proportion of subjects who had a best response rating over the whole duration of the study of CR or PR according to RECIST v.1.1. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[4]	10[5]		
Units: Count of subjects				
Responder	0	0		
Non-Responder	6	10		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: ORR According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	ORR According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

The investigator’s assessment of ORR according to mRECIST and RECIST 1.1 was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR or

PR. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[6]	10[7]		
Units: Count of subjects				
Responder (mRECIST)	0	1		
Non-Responder (mRECIST)	6	9		
Responder (RECIST v.1.1)	0	1		
Non-Responder (RECIST v.1.1)	6	9		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point title	Disease Control Rate (DCR) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point description:

DCR was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR, PR or stable disease (SD) according to mRECIST and RECIST 1.1 criteria. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Subjects prematurely discontinuing without an assessment was considered non-responders for the analysis.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[8]	10[9]		
Units: Count of subjects				
Responder (mRECIST)	2	5		
Non-Responder (mRECIST)	4	5		
Responder (RECIST v.1.1)	2	5		
Non-Responder (RECIST v.1.1)	4	5		

Notes:

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: DCR According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	DCR According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

DCR was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR, PR or stable disease (SD) according to mRECIST and RECIST 1.1 criteria. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Subjects prematurely discontinuing without an assessment was considered non-responders for the analysis.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[10]	10[11]		
Units: Count of subjects				
Responder (mRECIST)	3	4		
Non-Responder (mRECIST)	3	6		
Responder (RECIST v.1.1)	3	4		
Non-Responder (RECIST v.1.1)	3	6		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first day with study drug intake until death from any cause or until the last date the subject was known to be alive. In the below table, "99999" indicates that data was not estimable due to censored data.

End point type	Secondary

End point timeframe:

From start of study treatment until death from any cause or until the last date the subject was known to be alive (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[12]	10[13]		
Units: Days				
median (confidence interval 95%)	99 (39 to 99999)	427 (36 to 99999)		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Radiographic Tumor Progression (TTRP) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point title	Time to Radiographic Tumor Progression (TTRP) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point description:

TTRP was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of the first observed radiographic disease progression. In the below table, "99999" indicates that data was not estimable due to censored data.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[14]	10[15]		
Units: Days				
median (confidence interval 95%)				
mRECIST	42 (39 to 99999)	167 (42 to 99999)		
RECIST v.1.1	42 (39 to 99999)	126 (42 to 132)		

Notes:

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: TTRP According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	TTRP According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

TTRP was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of the first observed radiographic disease progression.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[16]	10[17]		
Units: Days				
median (confidence interval 95%)				
mRECIST	56 (28 to 84)	84 (42 to 167)		
RECIST v.1.1	56 (28 to 84)	84 (42 to 167)		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	Duration of Response (DOR) According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

DOR was defined as the time from the date of first objective radiological response to the date where PD was first documented radiologically or death (if death occurred first).

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	10		
Units: Days				
mRECIST	0	83		
RECIST v.1.1	0	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response Assessed by Central Radiological Review and Investigator

End point title	Time to Objective Response Assessed by Central Radiological Review and Investigator

End point description:

Time to objective response was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) until the date when an objective tumor response (CR or PR) was first documented. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[18]	0[19]		
Units: Days				
median (confidence interval 95%)	(to)	(to)		

Notes:

[18] - No objective tumor responses were observed in this study.

[19] - No objective tumor responses were observed in this study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tumor Size Assessed by Central Radiological Review and Investigator

End point title	Change in Tumor Size Assessed by Central Radiological Review and Investigator

End point description:

Number of participants with a determined best change in tumor size. Due to database constraints, best percent change in target lesions from baseline by mRECIST independent assessments(Reader 1 and Reader 2) and investigator assessments are displayed in the charts uploaded as attachment.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Refametinib 50 mg BID + Sorafenib 400 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Reader 1	13			
Reader 2	12			
Investigator	10			

Attachments (see zip file)	Best percent change in target lessions by mRECIST/Best

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point title	Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point description:

The overall best response was defined as the best response recorded from date of the first dose of study treatment (refametinib or sorafenib) until the end of treatment. In the below table, "99999" indicates that no overall response were observed.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[20]	10[21]		
Units: Percentage of subjectes				
number (confidence interval 95%)				
mRECIST - Unconfirmed PR	16.7 (0.42 to 64.12)	20.0 (2.52 to 55.61)		

mRECIST - SD	16.7 (0.42 to 64.12)	30.0 (6.67 to 65.25)		
mRECIST - PD	50.0 (11.81 to 88.19)	20.0 (2.52 to 55.61)		
mRECIST - Not Evaluable	16.7 (0.42 to 64.12)	99999 (99999 to 99999)		
mRECIST - Missing	99999 (99999 to 99999)	30.0 (6.67 to 65.25)		
RECIST v.1.1 - Unconfirmed PR	16.7 (0.42 to 64.12)	99999 (99999 to 99999)		
RECIST v.1.1 - SD	16.7 (0.42 to 64.12)	50.0 (18.71 to 81.29)		
RECIST v.1.1 - PD	50.0 (11.81 to 88.19)	20.0 (2.52 to 55.61)		
RECIST v.1.1 - Not Evaluable	16.7 (0.42 to 64.12)	99999 (99999 to 99999)		
RECIST v.1.1 - Missing	99999 (99999 to 99999)	30.0 (6.67 to 65.25)		

Notes:

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

The overall best response was defined as the best response recorded from date of the first dose of study treatment (refametinib or sorafenib) until the end of treatment.In the below table, “99999” indicates that no overall response were observed.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[22]	10[23]		
Units: Percentage of subjects				
number (confidence interval 95%)				
mRECIST - PR	99999 (99999 to 99999)	10.0 (0.25 to 44.50)		
mRECIST - Unconfirmed PR	16.7 (0.42 to 64.12)	99999 (99999 to 99999)		
mRECIST - SD	33.3 (4.33 to 77.72)	30.0 (6.67 to 65.25)		
mRECIST - PD	50.0 (11.81 to 88.19)	30.0 (6.67 to 65.25)		
mRECIST – Missing	99999 (99999 to 99999)	30.0 (6.67 to 65.25)		

RECIST v.1.1 - PR	99999 (99999 to 99999)	10.0 (0.25 to 44.50)		
RECIST v.1.1 - Unconfirmed PR	16.7 (0.42 to 64.12)	99999 (99999 to 99999)		
RECIST v.1.1 - SD	33.3 (4.33 to 77.72)	30.0 (6.67 to 65.25)		
RECIST v.1.1 - PD	50.0 (11.81 to 88.19)	30.0 (6.67 to 65.25)		
RECIST v.1.1 - Missing	99999 (99999 to 99999)	30.0 (6.67 to 65.25)		

Notes:

[22] - FAS

[23] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point title	Progression-Free Survival (PFS) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

End point description:

PFS was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of first observed disease progression (radiological or clinical, whichever was first) or death due to any cause, if death occurs before progression was documented. In the below table, "99999" indicates that data was not estimable due to censored data.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[24]	10[25]		
Units: Days				
median (confidence interval 95%)				
mRECIST	42 (39 to 99)	84 (36 to 99999)		
RECIST v.1.1	42 (39 to 99999)	126 (36 to 132)		

Notes:

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point title	PFS According to mRECIST and RECIST v.1.1 Assessed by Investigator

End point description:

PFS was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of first observed disease progression (radiological or clinical, whichever was first) or death due to any cause, if death occurs before progression was documented. In the below table, "99999" indicates that data was not estimable due to censored data.

End point type	Secondary

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[26]	10[27]		
Units: Days				
median (confidence interval 95%)				
mRECIST	53 (14 to 84)	65 (36 to 167)		
RECIST v.1.1	53 (14 to 84)	65 (36 to 167)		

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An adverse event (AE) was any untoward medical occurrence in subject after providing written informed consent for participation in the study. AE may or may not be temporally or causally associated with the use of a medicinal product. A serious adverse event (SAE) was an AE resulting in any of following outcomes or deemed significant for any other reason: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly / birth defect; and another medical important serious event as judged by investigator. Treatment-emergent adverse events (TEAEs) were defined as adverse events that started or worsened after the start of study drug administration up to 30 (+5) days after last administration of the study medication.

End point type	Secondary

End point timeframe:

From start of study treatment up 30 (+5) days after the last administration of study treatment; Subjects were contacted every 3 months to determine survival status, if applicable (approximately 3.5 years)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[28]	10[29]		
Units: Count of subjects				
TEAE	6	10		
TESAE	6	7		

Notes:

[28] - SAF

[29] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) at Stage 2

End point title	Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) at Stage 2

End point description:

The FACT-Hep (version 4) was a 45 item, self-administered, multi-dimensional, psychometrically sound questionnaire developed to measure the quality of life (QoL) in subjects with hepatobiliary cancers, including metastatic colorectal cancer, hepatocellular carcinoma (HCC), and pancreatic, gallbladder and bile duct cancer. The FACT-Generic (FACT-G) contains 27 core questionnaires designed to measure general aspects of HRQoL of subjects with any form of cancer. Hepatobiliary Cancer Subscale (HCS) contains 18 questionnaires, designed to measure specific concerns/problems related to QoL in subjects with hepatobiliary cancers. It contains 5 domains: Physical Well-Being (PWB), Social Well-Being (SWB), Emotional Well-Being (EWB), Functional Well- Being (FWB), and HCS. The FACT-Hep total score was the sum of PWB, SWB, EWB, FWB and HCS domain scores ranging from 0 to 180. Higher score means better HRQoL.

End point type	Other pre-specified

End point timeframe:

Stage On Day 1 of Cycle 1, 2, 3 and EOT (within 7 days after last drug administration)

End point values	Asia population	RoW population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[30]	0[31]		
Units: Score on a scale				

Notes:

[30] - Data was not reported for this endpoint, since stage 2 analysis of the study was not performed.

[31] - Data was not reported for this endpoint, since stage 2 analysis of the study was not performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring from start of study treatment up 30 (+5) days after the last administration of study treatment. Subjects were contacted every 3 months to determine survival status, if applicable (approximately 3.5 years)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Rest of world (RoW) population

Reporting group description:

Rest of world (RoW) population: RoW subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

Reporting group title	Asia population

Reporting group description:

Asia population: Asian subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

Serious adverse events	Rest of world (RoW) population	Asia population	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	6 / 6 (100.00%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	2	1	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 10 (20.00%)	4 / 6 (66.67%)	
occurrences causally related to treatment / all	2 / 6	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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			
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rest of world (RoW) population	Asia population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	7 / 10 (70.00%)	6 / 6 (100.00%)	
occurrences (all)	18	13	
Diabetic macroangiopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Chills			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	6 / 10 (60.00%)	4 / 6 (66.67%)	
occurrences (all)	11	4	
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	4 / 10 (40.00%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Pleural effusion			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Confusional state			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Organic brain syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	5	2	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 10 (40.00%)	4 / 6 (66.67%)	
occurrences (all)	13	6	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 10 (20.00%)	3 / 6 (50.00%)	
occurrences (all)	2	9	
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood creatinine increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)		
occurrences (all)	1	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)		
occurrences (all)	1	2		
C-reactive protein increased				
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)		
occurrences (all)	1	0		
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)		
occurrences (all)	1	0		
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)		
occurrences (all)	5	1		
Haemoglobin decreased				
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)		
occurrences (all)	1	0		
Lipase increased				
subjects affected / exposed	0 / 10 (0.00%)	3 / 6 (50.00%)		
occurrences (all)	0	3		
Lymphocyte count decreased				
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)		
occurrences (all)	0	2		
Neutrophil count decreased				
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)		
occurrences (all)	0	1		
Platelet count decreased				
subjects affected / exposed	0 / 10 (0.00%)	3 / 6 (50.00%)		
occurrences (all)	0	7		
Weight decreased				
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)		
occurrences (all)	0	4		
Weight increased				

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Child-Pugh-Turcotte score increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Disturbance in attention			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dysarthria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Hepatic encephalopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sciatica			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	
occurrences (all)	1	3	
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Visual acuity reduced			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Chorioretinopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Abdominal pain upper			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Anal ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	
occurrences (all)	3	2	
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	7 / 10 (70.00%)	3 / 6 (50.00%)	
occurrences (all)	15	16	
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Toothache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vomiting			

subjects affected / exposed	4 / 10 (40.00%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Dermatitis acneiform			
subjects affected / exposed	2 / 10 (20.00%)	4 / 6 (66.67%)	
occurrences (all)	3	8	
Dry skin			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Pain of skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	2	3	
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	4 / 10 (40.00%)	1 / 6 (16.67%)	
occurrences (all)	10	1	
Rash maculo-papular			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nail ridging			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Urinary incontinence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Diabetic nephropathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Flank pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neck pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Spinal osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Dermatitis infected			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Tinea versicolour			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 6 (50.00%)	
occurrences (all)	4	4	
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	4	
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Hypoproteinaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			

subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 7	1 / 6 (16.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2013	1. Wording regarding use of refametinib tablets was clarified; -based on final pharmacokinetic results from a clinical relative bioavailability study (15221) where tablets exhibited comparable bioavailability to capsules, refametinib tablets could be used in clinical trials as an alternative for capsules. 2. Exclusion criteria were amended; -Subjects with a QTc greater than 480 milliseconds at the time of screening were excluded from the study due to the potential for QT prolongation with sorafenib -Exclusion criterion regarding women of childbearing potential was amended to reduce the time gap between the pregnancy evaluation and the beginning of treatment. -Exclusion criterion regarding systemic anticancer therapy was clarified, as subjectswith prior systemic anticancer therapy were not eligible for this study. 3. A dose modification scheme for hepatotoxic events was included, since hepatotoxicity is an “identified risk” for the refametinib-sorafenib combination. 4. Guidance regarding reporting of contrast media was added. 5. Additional safety electrocardiograms (ECGs) were added in order to characterize the cardiovascular safety at anticipated maximum plasma concentrations of the study treatment.

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.

Occurrence of "±” in relation with geometric CV is auto-generated. Decimal places were automatically truncated if last decimal equals zero. Biomarker and PK anlysis were defined as additional objectives/variables of this study.

Notes: