



Clinical trial results:

A multi-center, phase I/II study of BAY86-9766 in combination with gemcitabine in patients with locally advanced inoperable or metastatic pancreatic cancer

Summary

EudraCT number	2010-019588-12
Trial protocol	DE BE GB CZ IT
Global end of trial date	01 August 2013

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	04 July 2015

Trial information

Trial identification

Sponsor protocol code	BAY86-9766/14905
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01251640
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	01 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:

- Determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) of BAY 86-9766 to be investigated in combination with the standard gemcitabine regimen in the subsequent Phase II part of this study

Phase II

- Determine the efficacy of the combination BAY 86-9766 / gemcitabine in terms of the overall response rate (confirmed complete response + partial response) according to response evaluation criteria in solid tumors (RECIST) Version 1.1

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. 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:

Gemcitabine was administered on Day 1 at a dose of 1000 milligram per meter square (mg/m²) of body surface area intravenous (IV) infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent).

Evidence for comparator: -

Actual start date of recruitment	01 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 6

Worldwide total number of subjects	90
EEA total number of subjects	84

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)	52
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 study centers in 9 countries (8 countries in Europe, and the United States). The first patient's first visit was on 01 January 2011 and the cut-off date for the final analysis was 01 August 2013, when last patient's last visit occurred.

Pre-assignment

Screening details:

Total of 121 subjects were screened, out of which 31 subjects failed screening. Ninety subjects were assigned to treatment. Subjects assigned to Phase 1 were reported separately from Phase 2. Ten evaluable subjects originally assigned to the 50 milligram (mg) arm of Phase 1 were subsequently reported also under the Phase 2 and so accounted for twice.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Refametinib (BAY86-9766), 30 mg twice daily, Phase I

Arm description:

Refametinib was administered orally on Day 2 at a dose of 30 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 milligram per meter square (mg/m²) of body surface area intravenous (IV) infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks, thereafter, 3 out of 4 weeks. The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Investigational medicinal product name	Refametinib
Investigational medicinal product code	BAY86-9766
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Refametinib was administered orally at a dose of 30 mg twice daily during the treatment cycle.

Arm title	Refametinib (BAY86-9766), 50 mg twice daily, Phase I
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Arm description:

Refametinib was administered orally on Day 2 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

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

Dosage and administration details:

Refametinib was administered orally at a dose of 50 mg twice daily during the treatment cycle.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks, thereafter, 3 out of 4 weeks. The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Arm title	Refametinib (BAY86-9766), 50 mg twice daily, Phase II
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Arm description:

Refametinib was administered orally on Day 1 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Ten evaluable subjects originally assigned to the 50 mg arm of Phase I were subsequently reported also under the Phase II and so accounted for twice.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks, thereafter, 3 out of 4 weeks. The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Investigational medicinal product name	Refametinib
Investigational medicinal product code	BAY86-9766
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Refametinib was administered orally at a dose of 50 mg twice daily during the treatment cycle.

Number of subjects in period 1	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II
Started	10	10	80
Treated	10	10	80
Survival follow up	9	9	64
Safety follow up	10	10	74

Terminated treatment	10	10	80
Completed	0	0	0
Not completed	10	10	80
Progressive disease – radiological progression	5	2	26
AE associated with clinical disease progression	1	-	4
Consent withdrawn by subject	-	1	8
Physician decision	-	-	2
Death	-	-	6
Switching to another therapy	-	-	1
AE unassociated with clinical disease progression	3	7	31
Progressive disease – clinical progression	1	-	2

Baseline characteristics

Reporting groups

Reporting group title	Refametinib (BAY86-9766), 30 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 30 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 milligram per meter square (mg/m²) of body surface area intravenous (IV) infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Reporting group title	Refametinib (BAY86-9766), 50 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

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

Refametinib was administered orally on Day 1 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Ten evaluable subjects originally assigned to the 50 mg arm of Phase I were subsequently reported also under the Phase II and so accounted for twice.

Reporting group values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II
Number of subjects	10	10	80
Age categorical Units: Subjects			
Age 18 to less than or equal to 65 years	5	5	50
Age more than 65 years	5	5	30
Age continuous Units: years			
arithmetic mean	59.9	64.2	62.7
standard deviation	± 13.9	± 8.8	± 9.4
Gender categorical Units: Subjects			
Female	4	3	36
Male	6	7	44
Tumor node metastases (TNM) Classification at study entry			
TNM was based on size of tumor, if cancer cells had spread to nearby lymph nodes (LN), or distant (to other parts of the body) metastasis had occurred. Stages included: stage 0(no evidence of cancer cells), stage 1(T1N0M0), stage IIA(T0N1M0, T1N1M0, T2N0M0), stage IIB(T2N1M0, T3N0M0), stage III(any TN3M0), stage IV(anyT anyNM1), where T0=early form of tumor, T1= <2 centimeter(cm), T2=2-5 cm, T3= >2 cm, T4=large sized tumor, N0=not spread to LN, N1=spread to 1 to 3, N2=spread to 4 to 9, N3=spread >10 axillary LN, M0=no metastasis, M1= Metastasis.			
Units: Subjects			
Stage IIA	0	0	1
Stage IIB	1	0	1
Stage III	1	2	10

Stage IV	8	8	68
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Reporting group values	Total		
Number of subjects	90		
Age categorical Units: Subjects			
Age 18 to less than or equal to 65 years	52		
Age more than 65 years	38		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	40		
Male	50		
Tumor node metastases (TNM) Classification at study entry			
TNM was based on size of tumor, if cancer cells had spread to nearby lymph nodes (LN), or distant (to other parts of the body) metastasis had occurred. Stages included: stage 0(no evidence of cancer cells), stage 1(T1N0M0), stage IIA(T0N1M0, T1N1M0, T2N0M0), stage IIB(T2N1M0, T3N0M0), stage III(any TN3M0), stage IV(anyT anyNM1), where T0=early form of tumor, T1= <2 centimeter(cm), T2=2-5 cm, T3= >2 cm, T4=large sized tumor, N0=not spread to LN, N1=spread to 1 to 3, N2=spread to 4 to 9, N3=spread >10 axillary LN, M0=no metastasis, M1= Metastasis.			
Units: Subjects			
Stage IIA	1		
Stage IIB	2		
Stage III	11		
Stage IV	76		

End points

End points reporting groups

Reporting group title	Refametinib (BAY86-9766), 30 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 30 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 milligram per meter square (mg/m²) of body surface area intravenous (IV) infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Reporting group title	Refametinib (BAY86-9766), 50 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

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

Refametinib was administered orally on Day 1 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² of body surface area IV infusion dose over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Ten evaluable subjects originally assigned to the 50 mg arm of Phase I were subsequently reported also under the Phase II and so accounted for twice.

Subject analysis set title	Safety analysis set (SAF) population: Phase I
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Subject analysis set type	Safety analysis
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Subject analysis set description:

SAF population included all subjects who was assigned to study treatment with at least one intake of study drug.

Subject analysis set title	Maximum tolerated dose (MTD) population: Phase I
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

MTD population included all SAF subjects fully evaluable for occurrence of dose limiting toxicities (DLTs).

Subject analysis set title	Per protocol set (PPS) population: Phase II
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Subject analysis set type	Per protocol
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Subject analysis set description:

PPS population included all subjects who was assigned to treatment with no major protocol deviations for whom the primary efficacy variable was assessable.

Subject analysis set title	Refametinib (BAY86-9766),dose escalation 30 mg, 50 mg, Phase I
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects who received refametinib 30 mg twice daily during the treatment cycle and 50 mg twice daily during the treatment cycle.

Primary: Number of Subjects With Dose Limiting Toxicities (DLT): Phase I

End point title	Number of Subjects With Dose Limiting Toxicities (DLT): Phase I ^{[1][2]}
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End point description:

DLT were defined using National Cancer Institute Common Toxicity Criteria (CTC) Adverse Event (NCI CTCAE) version 4.0 as, Hematologic Toxicity: Grade 4 anemia, Grade 4 neutropenia lasting greater than (>) 10 days, Grade 3/4 neutropenia with fever >101 degree Fahrenheit, thrombocytopenia/Grade 3/4 thrombocytopenia with serious bleeding, or signs of serious bleeding and/or International Normalized Ratio >2.5 upper limit of normal (ULN) and/or partial thromboplastin time elevation of >2.5 ULN; Non-hematological toxicity: greater than or equal to (>=) Grade 3 toxicity, diarrhea only if refractory to

maximal antidiarrheal therapy, skin toxicity Grade 3 for >2 weeks and Grade 4, missing >14 consecutive daily doses of BAY86-9766 due to drug-related toxicity, aspartate/alanine aminotransferase increase from Grade 1 to Grade 2-4, or from Grade 2 (in subjects with liver metastases) to Grade 3-4 in case of: 2nd occurrence after a 1st recovery to baseline level taking >14 days; or 3rd occurrence.

End point type	Primary
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End point timeframe:

From randomization up to the first 8 weeks of therapy

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: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[3]	6 ^[4]		
Units: subjects				
No	5	5		
Yes	1	1		

Notes:

[3] - MTD analysis set included all safety analysis set subjects fully evaluable for occurrence of DLTs.

[4] - MTD analysis set included all safety analysis set subjects fully evaluable for occurrence of DLTs.

Statistical analyses

No statistical analyses for this end point

Primary: Tumor Response (Adjudicated Blinded Read Assessment): Phase II

End point title	Tumor Response (Adjudicated Blinded Read Assessment): Phase II ^[5] ^[6]
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End point description:

Tumor Response (= Best Overall Response) of a subject was defined as the best tumor response [Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD)] observed during trial period assessed according to the RECIST v 1.1 criteria. The subject's best overall response assignment was depended on the findings of both target and non-target disease and also on the appearance of new lesions.

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.

The blinded readers who were board certified, experienced and independent radiologists with broad expertise in oncology, radiology performed image evaluation independent from the conduct of the clinical part of the study.

End point type	Primary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

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

Justification: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistical analysis was not performed since as planned all continuous and ordinal

categorical variables were analyzed by descriptive statistics only.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[7]			
Units: percentage of subjects				
number (confidence interval 75%)				
Partial response	23.3 (16.89 to 30.99)			
Stable disease	38.3 (30.63 to 46.57)			
Unconfirmed Partial response	11.7 (7 to 18.15)			
Progressive disease	10 (5.69 to 16.23)			
Missing	16.7 (11.12 to 23.76)			

Notes:

[7] - Primary analysis set (PAS) included the first 60 per protocol set (PPS) subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Response: Investigator Assessment: Phase I

End point title	Tumor Response: Investigator Assessment: Phase I ^[8]
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End point description:

Tumor Response (= Best Overall Response) of a subject was defined as the best tumor response [CR, PR, SD, or PD] observed during trial period assessed according to the RECIST v 1.1 criteria. The subject's best overall response assignment was depended on the findings of both target and non-target disease and also on the appearance of new lesions.

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. '99999' in the reported data indicates that there were no subjects with those responses.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The statistical analysis was performed for each arm and reported under different endpoints. Hence not all the arms in the baseline period were reporting statistics in this endpoint.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[9]	10 ^[10]		
Units: percentage of subjects				
number (confidence interval 75%)				

Partial response	20 (6.22 to 42.9)	20 (6.22 to 42.9)		
Stable disease	50 (28.45 to 71.55)	40 (20.23 to 62.68)		
Unconfirmed Partial response	20 (6.22 to 42.9)	10 (1.33 to 31.67)		
Unconfirmed Stable disease	10 (1.33 to 31.67)	0 (0 to 0)		
Progressive disease	0 (0 to 0)	10 (1.33 to 31.67)		
Missing	0 (0 to 0)	20 (6.22 to 42.9)		

Notes:

[9] - Safety analysis set (SAF) included all subjects with at least one drug dose.

[10] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC): Phase I

End point title	Disease Control (DC): Phase I ^[11]
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End point description:

Disease control rate (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 SD according to RECIST (Version 1.1). SD had to be maintained for at least six weeks from the first demonstration of that rating.

Confirmed DCR included unconfirmed CR or PR which is more than 6 weeks from the first dosing date and unconfirmed DCR included unconfirmed CR or PR which is less than 6 weeks from the first dosing date.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[12]	10 ^[13]		
Units: percentage of subjects				
number (confidence interval 75%)				
Confirmed DCR	90 (68.33 to 98.67)	70 (46.85 to 87.25)		
Unconfirmed DCR	10 (1.33 to 31.67)	0 (0 to 0)		

Notes:

[12] - SAF included all subjects with at least one drug dose.

[13] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC): Phase II

End point title	Disease Control (DC): Phase II ^[14]
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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 SD according to RECIST (Version 1.1). SD had to be maintained for at least six weeks from the first demonstration of that rating.

Confirmed DCR included unconfirmed CR or PR which is more than 6 weeks from the first dosing date and unconfirmed DCR included unconfirmed CR or PR which is less than 6 weeks from the first dosing date.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[15]			
Units: percentage of subjects				
number (confidence interval 75%)				
Confirmed DCR	73.3 (65.47 to 80.13)			

Notes:

[15] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Phase I

End point title	Duration of Response (DOR): Phase I ^[16]
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End point description:

DOR defined as the time from first observed tumor response (CR or PR) until disease progression or until death caused by disease progression. Only confirmed responses were considered.

'99999' in the reported data indicates there were too few subjects in the data set, hence the data were not summarized.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[17]	10 ^[18]		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[17] - SAF included all subjects with at least one drug dose.

[18] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response: Phase II

End point title	Duration of Response: Phase II ^[19]
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End point description:

DOR defined as the time from first observed tumor response (CR or PR) until disease progression or until death caused by disease progression. Only confirmed responses were considered.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	10 ^[20]			
Units: days				
median (confidence interval 95%)	112 (84 to 265)			

Notes:

[20] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP): Phase I

End point title	Time to Progression (TTP): Phase I ^[21]
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End point description:

TTP defined as the time from randomization (in this study randomization refers to the date of treatment assignment) to the first observation of progressive disease (PD, RECIST Version 1.1) or to the last date of a definite assessment (not status Unknown), if the subject was progression-free until that assessment. Subjects without progression at the time of analysis were censored at their last date of tumor evaluation.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[22]	10 ^[23]		
Units: days				
median (confidence interval 95%)	275 (107 to 392)	168 (20 to 168)		

Notes:

[22] - SAF included all subjects with at least one drug dose.

[23] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP): Phase II

End point title	Time to Progression (TTP): Phase II ^[24]
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End point description:

TTP defined as the time from randomization (in this study randomization referred to the date of treatment assignment) to the first observation of progressive disease (PD, RECIST Version 1.1) or to the last date of a definite assessment (not status Unknown), if the subject was progression-free until that assessment. Subjects without progression at the time of analysis were censored at their last date of tumor evaluation.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[25]			
Units: days				
median (confidence interval 95%)	217 (140 to 278)			

Notes:

[25] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS): Phase I

End point title	Progression-Free Survival (PFS): Phase I ^[26]
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End point description:

PFS defined as the time from randomization (Randomization referred to the date of treatment assignment) to disease progression (radiological or clinical, whichever was earlier) or death (if death occurred before progression was documented). Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[27]	10 ^[28]		
Units: days				
median (confidence interval 95%)	163 (65 to 275)	267 (20 to 322)		

Notes:

[27] - SAF included all subjects with at least one drug dose.

[28] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS): Phase II

End point title	Progression-Free Survival (PFS): Phase II ^[29]
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End point description:

PFS defined as the time from randomization (Randomization referred to the date of treatment assignment) to disease progression (radiological or clinical, whichever was earlier) or death (if death occurred before progression was documented). Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[30]			
Units: days				
median (confidence interval 95%)	168 (115 to 225)			

Notes:

[30] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Phase I

End point title	Overall Survival (OS): Phase I ^[31]
End point description:	
Overall survival defined as the time from randomization (in this study randomization referred to the date of treatment assignment) until death from any cause or until the last date the subject was known to be alive. Subjects who were still alive at the time of analysis were censored at their last date of last contact.	
End point type	Secondary
End point timeframe:	
From start of treatment until 134 weeks assessed every 8 weeks	

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[32]	10 ^[33]		
Units: days				
median (confidence interval 95%)	355 (65 to 574)	270 (140 to 553)		

Notes:

[32] - SAF included all subjects with at least one drug dose.

[33] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Phase II

End point title	Overall Survival (OS): Phase II ^[34]
End point description:	
Overall survival defined as the time from randomization (in this study randomization referred to the date of treatment assignment) until death from any cause or until the last date the subject was known to be alive. Subjects who were still alive at the time of analysis were censored at their last date of last	

contact.

End point type	Secondary
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[35]			
Units: days				
median (confidence interval 95%)	270 (200 to 355)			

Notes:

[35] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose: Phase I

End point title	Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose: Phase I
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End point description:

MTD was determined by testing increasing doses up to 50 mg twice daily on dose escalation cohorts 1 to 2 with 3 subjects each. MTD reflects highest dose of drug that did not cause an unacceptable side effect (= DLT in more than 30% of subjects). The MTD was the dose at which at most, one in six subjects in Cycle 1 had a DLT. RP2D was depended on the results of the Phase I part of this study.

End point type	Other pre-specified
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End point timeframe:

From start of the treatment upto the first eight weeks of therapy

End point values	Refametinib (BAY86-9766),dose escalation 30 mg, 50 mg,			
Subject group type	Subject analysis set			
Number of subjects analysed	12 ^[36]			
Units: milligram(s)				
number (not applicable)				
MTD	50			
RP2D	50			

Notes:

[36] - MTD analysis set included all safety analysis set subjects fully evaluable for occurrence of DLTs.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Drug Concentration in Plasma (Cmax) of Refametinib and Metabolite

End point title	Maximum Observed Drug Concentration in Plasma (Cmax) of Refametinib and Metabolite ^[37]
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End point description:

Cmax refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Data for this outcome included subjects who received refametinib without gemcitabine at C1D21 and refametinib with gemcitabine at C1D22.

End point type	Other pre-specified
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End point timeframe:

Cycle (C) 1 Day (D) 21 (C1D21), C1D22

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[38]	10 ^[39]		
Units: microgram per liter				
geometric mean (geometric coefficient of variation)				
Refametinib: C1D21 (N= 8, 6)	489 (± 66)	1046 (± 37)		
Metabolite M-17: C1D21 (N= 8, 6)	82.9 (± 31)	175 (± 75)		
Refametinib: C1D22 (N= 8, 6)	511 (± 79)	900 (± 67)		
Metabolite M-17: C1D22 (N= 8, 6)	100 (± 30)	164 (± 108)		

Notes:

[38] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[39] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Drug Concentration in Plasma (Cmax) of Gemcitabine and its Metabolite

End point title	Maximum Observed Drug Concentration in Plasma (Cmax) of Gemcitabine and its Metabolite ^[40]
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End point description:

Cmax refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Data for this outcome included subjects who received gemcitabine without refametinib at C1D1 and gemcitabine with refametinib at C1D22.

End point type	Other pre-specified
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End point timeframe:

C1D1, C1D22

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[41]	10 ^[42]		
Units: milligram per liter				
geometric mean (geometric coefficient of variation)				
Gemcitabine: C1D1 (N=10, 10)	2.49 (± 163)	2.74 (± 197)		
Metabolite dFdU: C1D1 (N=10, 10)	28 (± 22)	26.6 (± 25)		
Gemcitabine: C1D22 (N=7, 5)	6.06 (± 88)	3.5 (± 248)		
Metabolite dFdU: C1D22 (N=7, 5)	26.2 (± 19)	21.5 (± 46)		

Notes:

[41] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[42] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Reach Maximum Drug Concentration in Plasma (Tmax) of Refametinib and Metabolite

End point title	Time to Reach Maximum Drug Concentration in Plasma (Tmax) of Refametinib and Metabolite ^[43]
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End point description:

Tmax refers to the time after dosing when a drug attains its highest measurable concentration (Cmax). It is obtained by collecting a series of blood samples at various times after dosing, and measuring them for drug content. Data for this outcome included subjects who received refametinib without gemcitabine at C1D21 and refametinib with gemcitabine at C1D22.

End point type	Other pre-specified
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End point timeframe:

C1D21, C1D22

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[44]	10 ^[45]		
Units: hours				
median (full range (min-max))				
Refametinib: C1D21 (N= 8, 6)	3.5 (2 to 4)	2 (1 to 4)		
Metabolite M-17: C1D21 (N= 8, 6)	4 (2 to 4)	2 (1 to 4)		
Refametinib: C1D22 (N= 8, 6)	2.8 (2 to 4.5)	1.8 (1 to 4.5)		
Metabolite M-17: C1D22 (N= 8, 6)	2.5 (2 to 4.5)	2 (1.6 to 8.5)		

Notes:

[44] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[45] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Reach Maximum Drug Concentration in Plasma (Tmax) of Gemcitabine and its Metabolite

End point title	Time to Reach Maximum Drug Concentration in Plasma (Tmax) of Gemcitabine and its Metabolite ^[46]
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End point description:

Tmax refers to the time after dosing when a drug attains its highest measurable concentration (Cmax). It is obtained by collecting a series of blood samples at various times after dosing, and measuring them for drug content. Data for this outcome included subjects who received gemcitabine without refametinib at C1D1 and gemcitabine with refametinib at C1D22.

End point type	Other pre-specified
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End point timeframe:

C1D1, C1D22

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[47]	10 ^[48]		
Units: hours				
median (full range (min-max))				
Gemcitabine: C1D1 (N=10, 10)	0.8 (0.5 to 1)	1 (0.4 to 1.5)		
Metabolite dFdU: C1D1 (N=10, 10)	1 (0.5 to 2)	1.2 (0.7 to 2.2)		
Gemcitabine: C1D22 (N=7, 5)	1 (0.5 to 1)	1 (0.5 to 1.2)		
Metabolite dFdU: C1D22 (N=7, 5)	1 (1 to 2)	1.2 (0.5 to 1.5)		

Notes:

[47] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[48] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

Other pre-specified: Area Under the Curve From Time Zero to Last Quantifiable Concentration AUC (0-tlast) of Refametinib and Metabolite

End point title	Area Under the Curve From Time Zero to Last Quantifiable Concentration AUC (0-tlast) of Refametinib and Metabolite ^[49]
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-tlast) is defined as AUC from time zero to the last data point above the lower limit of quantification (2.00 microgram per liter). Data for this outcome included subjects who received refametinib without gemcitabine at C1D21 and refametinib with gemcitabine at C1D22.

End point type	Other pre-specified
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End point timeframe:

C1D21, C1D22

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[50]	10 ^[51]		
Units: microgram*hour per liter				
geometric mean (geometric coefficient of variation)				
Refametinib: C1D21 (N= 8, 6)	2844 (± 80)	5186 (± 58)		
Metabolite M-17: C1D21 (N= 8, 6)	498 (± 28)	907 (± 68)		
Refametinib: C1D22 (N= 8, 6)	2979 (± 85)	4629 (± 65)		
Metabolite M-17: C1D22 (N= 8, 6)	595 (± 37)	850 (± 96)		

Notes:

[50] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[51] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under the Curve From Time Zero to Last Quantifiable Concentration AUC (0-tlast) of Gemcitabine and its Metabolite

End point title	Area Under the Curve From Time Zero to Last Quantifiable Concentration AUC (0-tlast) of Gemcitabine and its Metabolite ^[52]
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-tlast) is defined as AUC from time zero to the last data point above the lower limit of quantification (5.00 microgram per liter). Data for this outcome included subjects who received gemcitabine without refametinib at C1D1 and gemcitabine with refametinib at C1D22.

End point type	Other pre-specified
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End point timeframe:

C1D1, C1D22

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[53]	10 ^[54]		
Units: milligram*hour per liter				
geometric mean (geometric coefficient of variation)				
Gemcitabine: C1D1 (N=10, 10)	2.4 (± 117)	2.39 (± 132)		
Metabolite dFdU: C1D1 (N=10, 10)	198 (± 38)	143 (± 26)		
Gemcitabine: C1D22 (N=7, 5)	4.93 (± 81)	2.83 (± 177)		
Metabolite dFdU: C1D22 (N=7, 5)	212 (± 45)	146 (± 41)		

Notes:

[53] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[54] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under the Curve From Time Zero to 8 hours [AUC (0 -8)] of Refametinib and Metabolite

End point title	Area Under the Curve From Time Zero to 8 hours [AUC (0 -8)] of Refametinib and Metabolite ^[55]
End point description:	
AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC(0-8) is defined as area under the concentration from time zero to 8 hours. Data for this outcome included subjects who received refametinib without gemcitabine at C1D21 and refametinib with gemcitabine at C1D22.	
End point type	Other pre-specified
End point timeframe:	
C1D21, C1D22	

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[56]	10 ^[57]		
Units: microgram*hour per liter				
geometric mean (geometric coefficient of variation)				
Refametinib: C1D21 (N= 8, 6)	2857 (± 80)	5193 (± 58)		
Metabolite M-17: C1D21 (N= 8, 6)	499 (± 30)	909 (± 67)		

Refametinib: C1D22 (N= 8, 6)	2838 (± 85)	4457 (± 61)		
Metabolite M-17: C1D22 (N= 8, 6)	563 (± 31)	814 (± 87)		

Notes:

[56] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[57] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area under the Concentration-Time Curve (AUC) of Gemcitabine and its Metabolite

End point title	Area under the Concentration-Time Curve (AUC) of Gemcitabine and its Metabolite ^[58]
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End point description:

AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Data for this outcome included subjects who received gemcitabine without refametinib at C1D1 and gemcitabine with refametinib at C1D22. '99999' in the reported data indicates data for AUC was not calculated due to insufficient number of data points in the terminal phase.

End point type	Other pre-specified
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End point timeframe:

C1D1, C1D22

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[59]	10 ^[60]		
Units: milligram*hour per liter				
geometric mean (geometric coefficient of variation)				
Gemcitabine: C1D1 (N=1, 0)	99999 (± 99999)	99999 (± 99999)		
Metabolite dFdU: C1D1 (N=0, 1)	99999 (± 99999)	99999 (± 99999)		
Gemcitabine: C1D22 (N=1, 2)	99999 (± 99999)	9.344 (± 11.88)		
Metabolite dFdU: C1D22 (N=0, 0)	99999 (± 99999)	99999 (± 99999)		

Notes:

[59] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[60] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Half Life Associated With Terminal Slope (t1/2) of Refametinib and Metabolite

End point title	Half Life Associated With Terminal Slope (t1/2) of Refametinib and Metabolite ^[61]
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End point description:

T1/2 refers to the elimination of the drug. It is the time taken for the blood plasma concentration to reach half the concentration in the terminal phase of elimination. It is expressed in hours (h) and derived from the terminal slope of the concentration versus time curve. Data for this outcome included subjects who received refametinib without gemcitabine at C1D21 and refametinib with gemcitabine at C1D22.

'99999' in the reported data indicates data for t1/2 was not calculated due to insufficient number of data points in the terminal phase.

End point type	Other pre-specified
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End point timeframe:

C1D21, C1D22

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[62]	10 ^[63]		
Units: hour				
geometric mean (geometric coefficient of variation)				
Refametinib: C1D21 (N= 8, 6)	99999 (± 99999)	99999 (± 99999)		
Metabolite M-17: C1D21 (N= 8, 6)	99999 (± 99999)	99999 (± 99999)		
Refametinib: C1D22 (N= 8, 6)	99999 (± 99999)	99999 (± 99999)		
Metabolite M-17: C1D22 (N= 8, 6)	99999 (± 99999)	99999 (± 99999)		

Notes:

[62] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[63] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Half Life Associated With Terminal Slope (t1/2) of Gemcitabine and its Metabolite

End point title	Half Life Associated With Terminal Slope (t1/2) of Gemcitabine and its Metabolite ^[64]
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End point description:

T1/2 refers to the elimination of the drug. It is the time taken for the blood plasma concentration to reach half the concentration in the terminal phase of elimination. It is expressed in hours (h) and derived from the terminal slope of the concentration versus time curve. Data for this outcome included subjects who received gemcitabine without refametinib at C1D1 and gemcitabine with refametinib at C1D22.

'99999' in the reported data indicates data for t1/2 was not calculated due to insufficient number of data points in the terminal phase.

End point type	Other pre-specified
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End point timeframe:

C1D1, C1D22

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[65]	10 ^[66]		
Units: hour				
geometric mean (geometric coefficient of variation)				
Gemcitabine: C1D1 (N=10, 10)	99999 (± 99999)	99999 (± 99999)		
Metabolite dFdU: C1D1 (N=10, 10)	99999 (± 99999)	99999 (± 99999)		
Gemcitabine: C1D22 (N=7, 5)	99999 (± 99999)	99999 (± 99999)		
Metabolite dFdU: C1D22 (N=7, 5)	99999 (± 99999)	99999 (± 99999)		

Notes:

[65] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

[66] - In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Improvement or Deterioration in Worst Pain: Phase I

End point title	Number of Subjects With Improvement or Deterioration in Worst Pain: Phase I ^[67]
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End point description:

A minimally important difference (MID) for the 'worst' pain item of BPI-SF scale (11 point scale; range 0 [no pain] to 10 [worst pain]), had been estimated as a 2-point change. The proportions of subjects who have improved [a decrease of greater than or equal to (\geq) 2-points from baseline], remained stable (not reached a MID), deteriorated (an increase of \geq 2-points from baseline) scored by the 'worst' pain item were summarized at each time point.

End point type	Other pre-specified
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End point timeframe:

C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment visit

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[68]	10 ^[69]		
Units: subjects				
C1D29: Improved (N=7, 5)	4	2		
C1D29: Stable (N=7, 5)	3	3		
C1D29: Deteriorated (N=7, 5)	0	0		
C2D1: Improved (N=9, 6)	4	3		
C2D1: Stable (N=9, 6)	5	2		
C2D1: Deteriorated (N=9, 6)	0	1		
C3D1: Improved (N=5, 5)	2	3		
C3D1: Stable (N=5, 5)	3	1		
C3D1: Deteriorated (N=5, 5)	0	1		
C4D1: Improved (N=4, 3)	2	1		
C4D1: Stable (N=4, 3)	2	2		
C4D1: Deteriorated (N=4, 3)	0	0		
C5D1: Improved (N=4, 1)	2	0		
C5D1: Stable (N=4, 1)	2	1		
C5D1: Deteriorated (N=4, 1)	0	0		
C6D1: Improved (N=3, 1)	2	0		
C6D1: Stable (N=3, 1)	0	1		
C6D1: Deteriorated (N=3, 1)	1	0		
C7D1: Improved (N=4, 1)	2	0		
C7D1: Stable (N=4, 1)	2	0		
C7D1: Deteriorated (N=4, 1)	0	1		
C8D1: Improved (N=4, 0)	2	0		
C8D1: Stable (N=4, 0)	2	0		
C8D1: Deteriorated (N=4, 0)	0	0		
C9D1: Improved (N=4, 0)	1	0		
C9D1: Stable (N=4, 0)	2	0		
C9D1: Deteriorated (N=4, 0)	1	0		
C10D1: Improved (N=2, 0)	0	0		
C10D1: Stable (N=2, 0)	2	0		
C10D1: Deteriorated (N=2, 0)	0	0		
C11D1: Improved (N=2, 0)	0	0		
C11D1: Stable (N=2, 0)	2	0		
C11D1: Deteriorated (N=2, 0)	0	0		
C12D1: Improved (N=1, 0)	0	0		
C12D1: Stable (N= 1, 0)	1	0		
C12D1: Deteriorated (N=1, 0)	0	0		
C13D1: Improved (N=1, 0)	0	0		
C13D1: Stable (N=1, 0)	1	0		
C13D1: Deteriorated (N=1, 0)	0	0		
End of treatment visit: Improved (N=7, 7)	2	3		
End of treatment visit: Stable (N=7, 7)	5	4		
End of treatment visit: Deteriorated (N=7, 7)	0	0		

Notes:

[68] - SAF included all subjects with at least one drug dose.

[69] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Improvement or Deterioration in Worst Pain: Phase II

End point title	Number of Subjects With Improvement or Deterioration in Worst Pain: Phase II ^[70]
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End point description:

A MID for the 'worst' pain item of BPI-SF scale (11 point scale; range 0 [no pain] to 10 [worst pain]), had been estimated as a 2-point change. The proportions of subjects who have improved [a decrease of ≥ 2 -points from baseline], remained stable (not reached a MID), deteriorated (an increase of ≥ 2 -points from baseline) scored by the 'worst' pain item were summarized at each time point.

End point type	Other pre-specified
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End point timeframe:

C2D1, C4D1, C6D1, C8D1, C10D1, C12D1, End of treatment visit

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[71]			
Units: subjects				
C2D1: Improved (N=34)	16			
C2D1: Stable (N=34)	12			
C2D1: Deteriorated (N=34)	6			
C4D1: Improved (N=23)	8			
C4D1: Stable (N=23)	13			
C4D1: Deteriorated (N=23)	2			
C6D1: Improved (N=14)	4			
C6D1: Stable (N=14)	8			
C6D1: Deteriorated (N=14)	2			
C8D1: Improved (N=9)	2			
C8D1: Stable (N=9)	7			
C8D1: Deteriorated (N=9)	0			
C10D1: Improved (N=4)	1			
C10D1: Stable (N=4)	3			
C10D1: Deteriorated (N=4)	0			
C12D1: Improved (N=2)	1			
C12D1: Stable (N=2)	1			
C12D1: Deteriorated (N=2)	0			

End of treatment visit: Improved (N=34)	14			
End of treatment visit: Stable (N=34)	15			
End of treatment visit: Deteriorated (N=34)	5			

Notes:

[71] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Pain Response: Phase I

End point title	Number of Subjects With Pain Response: Phase I ^[72]
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End point description:

Number of subjects with pain response were classified as yes, no or unknown. Pain response yes indicates decrease of at least 2 points from baseline in worst pain, an item of BPI-SF scale (11 point scale; range 0 [no pain] to 10 [worst pain]), and no increase in pain medication score; no indicates decrease less than 2 points from baseline in worst pain, or increase in pain medication score; and unknown indicates 1. decrease at least 2 points from baseline in worst pain, but the change in pain medication score is unknown and 2. no increase in pain medication score, but decrease from baseline in worst pain is unknown.

End point type	Other pre-specified
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End point timeframe:

C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment visit

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[73]	10 ^[74]		
Units: subjects				
C1D29: No (N=9, 6)	3	3		
C1D29: Yes (N=9, 6)	4	1		
C1D29: Unknown (N=9, 6)	2	2		
C2D1: No (N=9, 6)	6	3		
C2D1: Yes (N=9, 6)	2	2		
C2D1: Unknown (N=9, 6)	1	1		
C3D1: No (N=5, 5)	3	2		
C3D1: Yes (N=5, 5)	1	2		
C3D1: Unknown (N=5, 5)	1	1		
C4D1: No (N=4, 3)	2	2		
C4D1: Yes (N=4, 3)	2	0		
C4D1: Unknown (N=4, 3)	0	1		
C5D1: No (N=4, 1)	2	1		
C5D1: Yes (N=4, 1)	2	0		
C5D1: Unknown (N=4, 1)	0	0		
C6D1: No (N=4, 1)	1	1		

C6D1: Yes (N=4, 1)	2	0		
C6D1: Unknown (N=4, 1)	1	0		
C7D1: No (N=4, 1)	2	1		
C7D1: Yes (N=4, 1)	2	0		
C7D1: Unknown (N=4, 1)	0	0		
C8D1: No (N=4, 0)	2	0		
C8D1: Yes (N=4, 0)	1	0		
C8D1: Unknown (N=4, 0)	1	0		
C9D1: No (N=4, 0)	3	0		
C9D1: Yes (N=4, 0)	1	0		
C9D1: Unknown (N=4, 0)	0	0		
C10D1: No (N=2, 0)	2	0		
C10D1: Yes (N=2, 0)	0	0		
C10D1: Unknown (N=2, 0)	0	0		
C11D1: No (N=2, 0)	2	0		
C11D1: Yes (N=2, 0)	0	0		
C11D1: Unknown (N=2, 0)	0	0		
C12D1: No (N=1, 0)	1	0		
C12D1: Yes (N=1, 0)	0	0		
C12D1: Unknown (N=1, 0)	0	0		
C13D1: No (N=1, 0)	1	0		
C13D1: Yes (N=1, 0)	0	0		
C13D1: Unknown (N=1, 0)	0	0		
End of treatment visit: No (N=7, 8)	6	4		
End of treatment visit: Yes (N=7, 8)	1	2		
End of treatment visit: Unknown (N=7, 8)	0	2		

Notes:

[73] - SAF included all subjects with at least one drug dose.

[74] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Pain Response: Phase II

End point title	Number of Subjects With Pain Response: Phase II ^[75]
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End point description:

Number of subjects with pain response were classified as yes, no or unknown. Pain response yes indicates decrease of at least 2 points from baseline in worst pain, an item of BPI-SF scale (11 point scale; range 0 [no pain] to 10 [worst pain]), and no increase in pain medication score; no indicates decrease less than 2 points from baseline in worst pain, or increase in pain medication score; and unknown indicates 1. decrease at least 2 points from baseline in worst pain, but the change in pain medication score is unknown and 2. no increase in pain medication score, but decrease from baseline in worst pain is unknown.

End point type	Other pre-specified
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End point timeframe:

C2D1, C4D1, C6D1, C8D1, C10D1, C12D1, End of treatment visit

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[76]			
Units: subjects				
C2D1: No (N=34)	18			
C2D1: Yes (N=34)	10			
C2D1: Unknown (N=34)	8			
C4D1: No (N=25)	16			
C4D1: Yes (N=25)	4			
C4D1: Unknown (N=25)	5			
C6D1: No (N=15)	10			
C6D1: Yes (N=15)	2			
C6D1: Unknown (N=15)	3			
C8D1: No (N=10)	7			
C8D1: Yes (N=10)	2			
C8D1: Unknown (N=10)	1			
C10D1: No (N=5)	3			
C10D1: Yes (N=5)	1			
C10D1: Unknown (N=5)	1			
C12D1: No (N=3)	1			
C12D1: Yes (N=3)	1			
C12D1: Unknown (N=3)	1			
End of treatment visit: No (N=37)	20			
End of treatment visit: Yes (N=37)	8			
End of treatment visit: Unknown (N=37)	9			

Notes:

[76] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Brief Pain Inventory – Short Form (BPI-SF) score: Phase I

End point title	Brief Pain Inventory – Short Form (BPI-SF) score: Phase I ^[77]
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End point description:

Patient Reported Outcomes (PROs) data, as measured by the BPI-SF and the pain medication diary. BPI-SF was a 15-item, self administered, clinically valid, reliable and responsive measure developed to assess pain related to cancer. The instrument was available in validated multilingual versions; on average, it requires less than 10 minutes to complete the questionnaire. BPI-SF is typically scored by averaging the pain severity score and overall pain interference score. Scores range from 0-10 and a higher score indicates a higher level of pain/interference. Data presented for BPI-SF as total score, pain severity score, pain interference score (PIS) and for the average of general activity, walking, and work [activity-related dimension], and of relations, mood, and enjoyment [mood-related dimension] at each assessment time point.

'99999' in the reported data indicates that there were no subjects evaluated at the specified time point.

End point type	Other pre-specified
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End point timeframe:

Baseline, C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment (EOT) visit

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[78]	10 ^[79]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: Pain severity score (N=10, 9)	2.95 (± 2.54)	2 (± 2.05)		
C1D29: Pain severity score (N=7, 6)	0.79 (± 0.81)	0.42 (± 0.68)		
C2D1: Pain severity score (N=9, 6)	1.31 (± 2.2)	1.04 (± 1.37)		
C3D1: Pain severity score (N=5, 5)	0.25 (± 0.43)	1.25 (± 1.21)		
C4D1: Pain severity score (N=4, 3)	0.25 (± 0.5)	0.33 (± 0.58)		
C5D1: Pain severity score (N=4, 1)	0.5 (± 1)	0 (± 99999)		
C6D1: Pain severity score (N=3, 1)	1 (± 1.73)	0 (± 99999)		
C7D1: Pain severity score (N=4, 1)	0.5 (± 1)	4.5 (± 99999)		
C8D1: Pain severity score (N=4, 0)	0.56 (± 1.13)	99999 (± 99999)		
C9D1: Pain severity score (N=4, 0)	1.13 (± 1.79)	99999 (± 99999)		
C10D1: Pain severity score (N=2, 0)	1 (± 1.41)	99999 (± 99999)		
C11D1: Pain severity score (N=2, 0)	0.75 (± 1.06)	99999 (± 99999)		
C12D1: Pain severity score (N=1, 0)	0 (± 99999)	99999 (± 99999)		
C13D1: Pain severity score (N=1, 0)	0 (± 99999)	99999 (± 99999)		
End of treatment: Pain severity score (N=7, 8)	0.93 (± 0.85)	1.16 (± 1.28)		
Baseline: PIS (N=10, 9)	2.7 (± 2.59)	1.98 (± 2.54)		
C1D29: PIS (N=7, 6)	1.41 (± 2.18)	0.48 (± 0.79)		
C2D1: PIS (N=9, 6)	1.41 (± 2.47)	1.52 (± 1.8)		
C3D1: PIS (N=5, 5)	0.4 (± 0.82)	1.91 (± 2.22)		
C4D1: PIS (N=4, 3)	0.64 (± 1.29)	2.05 (± 3.55)		
C5D1: PIS (N=4, 1)	0.57 (± 1.14)	0 (± 99999)		
C6D1: PIS (N=3, 1)	0.95 (± 1.65)	0 (± 99999)		
C7D1: PIS (N=4, 1)	0.57 (± 1.14)	5.57 (± 99999)		
C8D1: PIS (N=4, 0)	0.57 (± 1.14)	99999 (± 99999)		
C9D1: PIS (N=4, 0)	1.11 (± 1.69)	99999 (± 99999)		
C10D1: PIS (N=2, 0)	0.5 (± 0.71)	99999 (± 99999)		
C11D1: PIS (N=2, 0)	0.64 (± 0.91)	99999 (± 99999)		
C12D1: PIS (N=1, 0)	0 (± 99999)	99999 (± 99999)		
C13D1: PIS (N=1, 0)	0 (± 99999)	99999 (± 99999)		
End of treatment visit: PIS (N=7, 8)	1.53 (± 2.37)	1.86 (± 2.19)		

Baseline: PIS-activity-related dimension (N=10, 9)	2.73 (± 2.96)	1.96 (± 2.66)		
C1D29: PIS-activity-related dimension (N=7, 6)	1.67 (± 2.86)	0.33 (± 0.52)		
C2D1: PIS-activity-related dimension (N=9, 6)	1.37 (± 2.37)	1.44 (± 1.71)		
C3D1: PIS-activity-related dimension (N=5, 5)	0.47 (± 0.87)	1.93 (± 2.28)		
C4D1: PIS-activity-related dimension (N=4, 3)	0.5 (± 1)	1.33 (± 2.31)		
C5D1: PIS-activity-related dimension (N=4, 1)	0.58 (± 1.17)	0 (± 99999)		
C6D1: PIS-activity-related dimension (N=3, 1)	1 (± 1.73)	0 (± 99999)		
C7D1: PIS-activity-related dimension (N=4, 1)	0.58 (± 1.17)	7 (± 99999)		
C8D1: PIS-activity-related dimension (N=4, 0)	0.5 (± 1)	99999 (± 99999)		
C9D1: PIS-activity-related dimension (N=4, 0)	1.08 (± 1.57)	99999 (± 99999)		
C10D1: PIS-activity-related dimension (N=2, 0)	0.67 (± 0.94)	99999 (± 99999)		
C11D1: PIS-activity-related dimension (N=2, 0)	0.83 (± 1.18)	99999 (± 99999)		
C12D1: PIS-activity-related dimension (N=1, 0)	0 (± 99999)	99999 (± 99999)		
C13D1: PIS-activity-related dimension (N=1, 0)	0 (± 99999)	99999 (± 99999)		
EOT: PIS-activity-related dimension (N=7, 8)	1.67 (± 2.51)	1.58 (± 1.68)		
Baseline: PIS-mood-related dimension (N=10, 9)	2.33 (± 2.87)	1.93 (± 2.42)		
C1D29: PIS-mood-related dimension (N=7, 6)	1.38 (± 2.14)	0.61 (± 1.2)		
C2D1: PIS-mood-related dimension (9, 6)	1.56 (± 2.82)	1.89 (± 2.25)		
C3D1: PIS-mood-related dimension (N=5, 5)	0.33 (± 0.75)	1.87 (± 2.22)		
C4D1: PIS-mood-related dimension (N=4, 3)	0.67 (± 1.33)	2.67 (± 4.62)		
C5D1: PIS-mood-related dimension (N=4, 1)	0.5 (± 1)	0 (± 99999)		
C6D1: PIS-mood-related dimension (N=3, 1)	0.89 (± 1.54)	0 (± 99999)		
C7D1: PIS-mood-related dimension (N=4, 1)	0.5 (± 1)	5.67 (± 99999)		
C8D1: PIS-mood-related dimension (N=4, 0)	0.5 (± 1)	99999 (± 99999)		
C9D1: PIS-mood-related dimension (N=4, 0)	1.17 (± 1.91)	99999 (± 99999)		
C10D1: PIS-mood-related dimension (N=2, 0)	0.33 (± 0.47)	99999 (± 99999)		
C11D1: PIS-mood-related dimension (N=2, 0)	0.67 (± 0.94)	99999 (± 99999)		
C12D1: PIS-mood-related dimension (N=1, 0)	0 (± 99999)	99999 (± 99999)		
C13D1: PIS-mood-related dimension (N=1, 0)	0 (± 99999)	99999 (± 99999)		
EOT: PIS-mood-related dimension (N=7, 8)	1.67 (± 2.87)	2.04 (± 2.69)		

Notes:

[78] - SAF included all subjects with at least one drug dose.

[79] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Brief Pain Inventory – Short Form (BPI-SF) score: Phase II

End point title	Brief Pain Inventory – Short Form (BPI-SF) score: Phase II ^[80]
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End point description:

PROs data, as measured by the BPI-SF and the pain medication diary. BPI-SF was a 15-item, self administered, clinically valid, reliable and responsive measure developed to assess pain related to cancer. The instrument was available in validated multilingual versions; on average, it requires less than 10 minutes to complete the questionnaire. BPI-SF is typically scored by averaging the pain severity score and overall pain interference score. Scores range from 0-10 and a higher score indicates a higher level of pain/interference. Data presented for BPI-SF as total score, pain severity score, PIS and for the average of general activity, walking, and work [activity-related dimension], and of relations, mood, and enjoyment [mood-related dimension] at each assessment time point.

End point type	Other pre-specified
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End point timeframe:

Baseline, C1D1, C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment visit

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[81]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: Pain severity score (N=54)	1.64 (± 1.67)			
C1D1: Pain severity score (N=1)	3.5 (± 99999)			
C1D29: Pain severity score (N=39)	1.28 (± 1.66)			
C2D1: Pain severity score (N=36)	0.97 (± 1.63)			
C3D1: Pain severity score (N=30)	0.94 (± 1.51)			
C4D1: Pain severity score (N=23)	0.73 (± 1.39)			
C5D1: Pain severity score (N=23)	0.86 (± 1.78)			
C6D1: Pain severity score (N=15)	1.02 (± 2.52)			
C7D1: Pain severity score (N=12)	0.58 (± 1.32)			
C8D1: Pain severity score (N=10)	0.1 (± 0.32)			
C9D1: Pain severity score (N=9)	0.42 (± 0.64)			
C10D1: Pain severity score (N=5)	0.05 (± 0.11)			
C11D1: Pain severity score (N=3)	0 (± 0)			
C12D1: Pain severity score (N=3)	0.17 (± 0.29)			
C13D1: Pain severity score (N=1)	0 (± 99999)			

End of treatment: Pain severity score (N=37)	1.36 (± 2)			
Baseline: PIS (N=53)	1.62 (± 2.1)			
C1D1: PIS (N=1)	4.86 (± 99999)			
C1D29: PIS (N=39)	1.27 (± 2.17)			
C2D1: PIS (N=36)	1.22 (± 2.05)			
C3D1: PIS (N=29)	1.4 (± 1.91)			
C4D1: PIS (N=24)	1.08 (± 1.99)			
C5D1: PIS (N=23)	0.84 (± 1.96)			
C6D1: PIS (N=15)	0.93 (± 2.32)			
C7D1: PIS (N=12)	0.71 (± 1.62)			
C8D1: PIS (N=10)	0.34 (± 0.56)			
C9D1: PIS (N=9)	0.33 (± 0.6)			
C10D1: PIS (N=5)	0.06 (± 0.13)			
C11D1: PIS (N=3)	0 (± 0)			
C12D1: PIS (N=3)	0.1 (± 0.16)			
C13D1: PIS (N=1)	0 (± 99999)			
End of treatment visit: PIS (N=37)	2.01 (± 2.76)			
Baseline: PIS-activity-related dimension (N=52)	1.49 (± 2.32)			
C1D1: PIS-activity-related dimension (N=1)	5 (± 99999)			
C1D29: PIS-activity-related dimension (N=39)	1.22 (± 2.19)			
C2D1: PIS-activity-related dimension (N=36)	1.2 (± 2.03)			
C3D1: PIS-activity-related dimension (N=29)	1.41 (± 2.09)			
C4D1: PIS-activity-related dimension (N=24)	1.07 (± 2.07)			
C5D1: PIS-activity-related dimension (N=23)	0.8 (± 2.01)			
C6D1: PIS-activity-related dimension (N=15)	0.96 (± 2.52)			
C7D1: PIS-activity-related dimension (N=12)	1.08 (± 2.21)			
C8D1: PIS-activity-related dimension (N=10)	0.47 (± 0.79)			
C9D1: PIS-activity-related dimension (N=8)	0.33 (± 0.71)			
C10D1: PIS-activity-related dimension (N=5)	0 (± 0)			
C11D1: PIS-activity-related dimension (N=3)	0 (± 0)			
C12D1: PIS-activity-related dimension (N=3)	0.22 (± 0.38)			
C13D1: PIS-activity-related dimension (N=1)	0 (± 99999)			
EOT: PIS-activity-related dimension (N=37)	2.09 (± 2.86)			
Baseline: PIS-mood-related dimension (N=51)	1.5 (± 2.01)			
C1D1: PIS-mood-related dimension (N=1)	5.67 (± 99999)			
C1D29: PIS-mood-related dimension (N=39)	1.23 (± 2.26)			
C2D1: PIS-mood-related dimension (N=35)	1.19 (± 2.01)			

C3D1: PIS-mood-related dimension (N=29)	1.46 (± 1.95)			
C4D1: PIS-mood-related dimension (N=24)	1.17 (± 2.33)			
C5D1: PIS-mood-related dimension (N=23)	0.91 (± 2.08)			
C6D1: PIS-mood-related dimension (N=15)	0.87 (± 2.03)			
C7D1: PIS-mood-related dimension (N=12)	0.53 (± 1.63)			
C8D1: PIS-mood-related dimension (N=10)	0.3 (± 0.51)			
C9D1: PIS-mood-related dimension (N=9)	0.3 (± 0.51)			
C10D1: PIS-mood-related dimension (N=5)	0.07 (± 0.15)			
C11D1: PIS-mood-related dimension (N=3)	0 (± 0)			
C12D1: PIS-mood-related dimension (N=3)	0 (± 0)			
C13D1: PIS-mood-related dimension (N=1)	0 (± 99999)			
EOT: PIS-mood-related dimension (N=37)	1.92 (± 2.72)			

Notes:

[81] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Recorded Pain Medication in Diary: Phase I

End point title	Number of Subjects Recorded Pain Medication in Diary: Phase
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End point description:

Pain is directly associated with the use of analgesics. Therefore, a diary was also completed by the subjects to ensure all key information (that is, type of pain medication, dosage and frequency) related to the use of analgesics commonly used to control pain in pancreatic cancer was fully captured. Subjects were to record all pain medications taken during the last 48 hours, only, prior to their scheduled visit at the study site.

End point type	Other pre-specified
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End point timeframe:

Baseline, C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment visit

Notes:

[82] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase I arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[83]	10 ^[84]		
Units: subjects				
Baseline: No (N=10, 9)	0	0		

Baseline: Yes (N=10, 9)	10	9		
C1D29: No (N=9, 5)	3	0		
C1D29: Yes (N=9, 5)	6	5		
C2D1: No (N=9, 6)	1	0		
C2D1: Yes (N=9, 6)	8	6		
C3D1: No (N=5, 5)	0	1		
C3D1: Yes (N=5, 5)	5	4		
C4D1: No (N =4, 3)	0	0		
C4D1: Yes (N=4, 3)	4	3		
C5D1: No (N=4, 1)	0	0		
C5D1: Yes (N=4, 1)	4	1		
C6D1: No (N=4, 0)	0	0		
C6D1: Yes (N=4, 0)	4	0		
C7D1: No (N=4, 1)	0	0		
C7D1: Yes (N=4, 1)	4	1		
C8D1: No (N=4, 0)	0	0		
C8D1: Yes (N=4, 0)	4	0		
C9D1: No (N=4, 0)	0	0		
C9D1: Yes (N=4, 0)	4	0		
C10D1: No (N=2, 0)	0	0		
C10D1: Yes (N=2, 0)	2	0		
C11D1: No (N=2, 0)	0	0		
C11D1: Yes (N=2, 0)	2	0		
C12D1: No (N=1, 0)	0	0		
C12D1: Yes (N=1, 0)	1	0		
C13D1: No (N=1, 0)	0	0		
C13D1: Yes (N=1, 0)	1	0		
End of treatment visit: No (N=7, 8)	2	0		
End of treatment visit: Yes (N=7, 8)	5	8		

Notes:

[83] - SAF included all subjects with at least one drug dose.

[84] - SAF included all subjects with at least one drug dose.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Recorded Pain Medication in Diary: Phase II

End point title	Number of Subjects Recorded Pain Medication in Diary: Phase II ^[85]
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End point description:

Pain is directly associated with the use of analgesics. Therefore, a diary was also completed by the subjects to ensure all key information (that is, type of pain medication, dosage and frequency) related to the use of analgesics commonly used to control pain in pancreatic cancer was fully captured. Subjects were to record all pain medications taken during the last 48 hours, only, prior to their scheduled visit at the study site.

End point type	Other pre-specified
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End point timeframe:

Baseline, C1D29, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, End of treatment visit

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was related to Phase II arms only, hence not reporting statistics for all the arms in the baseline period.

End point values	Refametinib (BAY86-9766), 50 mg twice daily, Phase II			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[86]			
Units: subjects				
Baseline: No (N=57)	8			
Baseline: Yes (N=57)	49			
C1D29: No (N=43)	10			
C1D29: Yes (N=43)	33			
C2D1: No (N=35)	5			
C2D1: Yes (N=35)	30			
C3D1: No (N=29)	5			
C3D1: Yes (N=29)	24			
C4D1: No (N=24)	3			
C4D1: Yes (N=24)	21			
C5D1: No (N=23)	2			
C5D1: Yes (N=23)	21			
C6D1: No (N=14)	2			
C6D1: Yes (N=14)	12			
C7D1: No (N=14)	2			
C7D1: Yes (N=14)	12			
C8D1: No (N=11)	2			
C8D1: Yes (N=11)	9			
C9D1: No (N=9)	2			
C9D1: Yes (N=9)	7			
C10D1: No (N=4)	0			
C10D1: Yes (N=4)	4			
C11D1: No (N=3)	0			
C11D1: Yes (N=3)	3			
C12D1: No (N=3)	0			
C12D1: Yes (N=3)	3			
C13D1: No (N=1)	0			
C13D1: Yes (N=1)	1			
End of treatment visit: No (N=35)	6			
End of treatment visit: Yes (N=35)	29			

Notes:

[86] - PAS included the first 60 PPS subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with KRAS Mutational Status

End point title	Number of subjects with KRAS Mutational Status
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End point description:

End point type	Other pre-specified
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[87]	0 ^[88]	0 ^[89]	
Units: subjects				

Notes:

[87] - Finalized data is not available to report, and would be updated once report is finalized.

[88] - Finalized data is not available to report, and would be updated once report is finalized.

[89] - Finalized data is not available to report, and would be updated once report is finalized.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with the BRAF loci Mutational Status

End point title	Number of subjects with the BRAF loci Mutational Status
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End point description:

End point type	Other pre-specified
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End point timeframe:

From start of treatment until 134 weeks assessed every 8 weeks

End point values	Refametinib (BAY86-9766), 30 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[90]	0 ^[91]	0 ^[92]	
Units: subjects				

Notes:

[90] - Finalized data is not available to report, and would be updated once report is finalized.

[91] - Finalized data is not available to report, and would be updated once report is finalized.

[92] - Finalized data is not available to report, and would be updated once report is finalized.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Refametinib (BAY86-9766), 50 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² IV infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

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

Refametinib was administered orally on Day 1 at a dose of 50 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² IV infusion dose over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Reporting group title	Refametinib (BAY86-9766), 30 mg twice daily, Phase I
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Reporting group description:

Refametinib was administered orally on Day 2 at a dose of 30 mg twice daily during the treatment cycle. Gemcitabine was administered on Day 1 at a dose of 1000 mg/m² IV infusion over 30 minutes weekly for 7 out of 8 weeks (cycle 1), thereafter, 3 out of 4 weeks (cycle 2 and subsequent). The treatment was continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

Serious adverse events	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II	Refametinib (BAY86-9766), 30 mg twice daily, Phase I
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	48 / 70 (68.57%)	7 / 10 (70.00%)
number of deaths (all causes)	7	40	10
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 10 (0.00%)	4 / 70 (5.71%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	4 / 70 (5.71%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	4 / 70 (5.71%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Lung disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	5 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 70 (4.29%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	8 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood phosphorus decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Status epilepticus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	4 / 70 (5.71%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatotoxicity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dermatitis infected			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected dermal cyst			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	4 / 70 (5.71%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Peritonitis bacterial			

subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Refametinib (BAY86-9766), 50 mg twice daily, Phase I	Refametinib (BAY86-9766), 50 mg twice daily, Phase II	Refametinib (BAY86-9766), 30 mg twice daily, Phase I
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	69 / 70 (98.57%)	10 / 10 (100.00%)
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Embolism			
subjects affected / exposed	1 / 10 (10.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Deep vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	8 / 70 (11.43%)	1 / 10 (10.00%)
occurrences (all)	1	9	1
Hypertension			
subjects affected / exposed	3 / 10 (30.00%)	7 / 70 (10.00%)	2 / 10 (20.00%)
occurrences (all)	12	36	2
Jugular vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences (all)	2	3	0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	9 / 70 (12.86%)	0 / 10 (0.00%)
occurrences (all)	0	20	0
Chills			
subjects affected / exposed	1 / 10 (10.00%)	3 / 70 (4.29%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)	33 / 70 (47.14%)	8 / 10 (80.00%)
occurrences (all)	5	82	20
Influenza like illness			

subjects affected / exposed	1 / 10 (10.00%)	2 / 70 (2.86%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Malaise			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 10 (10.00%)	7 / 70 (10.00%)	1 / 10 (10.00%)
occurrences (all)	1	7	1
Mucosal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	15 / 70 (21.43%)	0 / 10 (0.00%)
occurrences (all)	0	42	0
Pyrexia			
subjects affected / exposed	6 / 10 (60.00%)	26 / 70 (37.14%)	4 / 10 (40.00%)
occurrences (all)	10	46	8
Pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 70 (2.86%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Oedema peripheral			
subjects affected / exposed	2 / 10 (20.00%)	39 / 70 (55.71%)	7 / 10 (70.00%)
occurrences (all)	2	84	17
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 10 (20.00%)	11 / 70 (15.71%)	1 / 10 (10.00%)
occurrences (all)	2	14	1
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	19 / 70 (27.14%)	0 / 10 (0.00%)
occurrences (all)	2	32	0
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	5 / 70 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	4 / 70 (5.71%) 4	0 / 10 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	8 / 70 (11.43%) 8	0 / 10 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	5 / 70 (7.14%) 6	0 / 10 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 70 (1.43%) 1	0 / 10 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 70 (4.29%) 3	0 / 10 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	8 / 70 (11.43%) 9	0 / 10 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 70 (2.86%) 2	1 / 10 (10.00%) 1
Confusional state subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	4 / 70 (5.71%) 6	1 / 10 (10.00%) 1
Sleep disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 70 (0.00%) 0	0 / 10 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 5	25 / 70 (35.71%) 74	4 / 10 (40.00%) 18
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 6	21 / 70 (30.00%) 73	3 / 10 (30.00%) 12
Blood albumin decreased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences (all)	0	2	7
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences (all)	0	8	1
Blood calcium decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 10 (10.00%)	14 / 70 (20.00%)	0 / 10 (0.00%)
occurrences (all)	6	40	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences (all)	0	6	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences (all)	0	1	3
Haemoglobin decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Lipase increased			
subjects affected / exposed	0 / 10 (0.00%)	5 / 70 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	10	0
Neutrophil count decreased			
subjects affected / exposed	3 / 10 (30.00%)	10 / 70 (14.29%)	3 / 10 (30.00%)
occurrences (all)	6	38	10
Prothrombin time shortened			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Platelet count decreased			

subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4	22 / 70 (31.43%) 62	4 / 10 (40.00%) 22
Protein total decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	1 / 10 (10.00%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	2 / 10 (20.00%) 2
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 70 (4.29%) 22	1 / 10 (10.00%) 16
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 70 (4.29%) 3	1 / 10 (10.00%) 1
Head injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	1 / 10 (10.00%) 1
Cardiac disorders Atrioventricular block subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 70 (1.43%) 1	0 / 10 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 3	1 / 10 (10.00%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	6 / 70 (8.57%) 7	1 / 10 (10.00%) 1
Burning sensation mucosal subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 70 (0.00%) 0	0 / 10 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	10 / 70 (14.29%) 10	0 / 10 (0.00%) 0
Encephalopathy			

subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Epilepsy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 10 (10.00%)	3 / 70 (4.29%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Metabolic encephalopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	3 / 70 (4.29%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Syncope			
subjects affected / exposed	2 / 10 (20.00%)	4 / 70 (5.71%)	0 / 10 (0.00%)
occurrences (all)	2	4	0
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	3 / 70 (4.29%)	1 / 10 (10.00%)
occurrences (all)	0	6	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 10 (20.00%)	40 / 70 (57.14%)	4 / 10 (40.00%)
occurrences (all)	2	178	29
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	9 / 70 (12.86%)	0 / 10 (0.00%)
occurrences (all)	0	47	0
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	26 / 70 (37.14%)	4 / 10 (40.00%)
occurrences (all)	1	121	27
Thrombocytopenia			
subjects affected / exposed	2 / 10 (20.00%)	30 / 70 (42.86%)	2 / 10 (20.00%)
occurrences (all)	3	118	6

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences (all)	0	17	3
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Retinopathy hypertensive			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 10 (30.00%)	19 / 70 (27.14%)	1 / 10 (10.00%)
occurrences (all)	4	26	5
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	9 / 70 (12.86%)	1 / 10 (10.00%)
occurrences (all)	0	16	1
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences (all)	0	11	1
Aphthous stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	3 / 10 (30.00%)	15 / 70 (21.43%)	2 / 10 (20.00%)
occurrences (all)	3	18	3
Dry mouth			
subjects affected / exposed	2 / 10 (20.00%)	9 / 70 (12.86%)	0 / 10 (0.00%)
occurrences (all)	3	13	0
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)	34 / 70 (48.57%)	4 / 10 (40.00%)
occurrences (all)	5	59	9
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	7 / 70 (10.00%)	2 / 10 (20.00%)
occurrences (all)	0	9	2
Faecal incontinence			

subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	2 / 70 (2.86%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	3 / 70 (4.29%)	3 / 10 (30.00%)
occurrences (all)	0	3	3
Nausea			
subjects affected / exposed	6 / 10 (60.00%)	33 / 70 (47.14%)	6 / 10 (60.00%)
occurrences (all)	10	66	9
Regurgitation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	11 / 70 (15.71%)	0 / 10 (0.00%)
occurrences (all)	1	20	0
Vomiting			
subjects affected / exposed	4 / 10 (40.00%)	31 / 70 (44.29%)	2 / 10 (20.00%)
occurrences (all)	9	61	3
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	1 / 70 (1.43%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Liver injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Portal vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	8 / 70 (11.43%)	0 / 10 (0.00%)
occurrences (all)	0	8	0
Dermatitis acneiform			
subjects affected / exposed	3 / 10 (30.00%)	9 / 70 (12.86%)	1 / 10 (10.00%)
occurrences (all)	5	19	2
Dry skin			
subjects affected / exposed	2 / 10 (20.00%)	7 / 70 (10.00%)	1 / 10 (10.00%)
occurrences (all)	2	13	1
Nail bed inflammation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Onychoclasia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	2 / 10 (20.00%)
occurrences (all)	0	10	2
Skin fissures			
subjects affected / exposed	2 / 10 (20.00%)	6 / 70 (8.57%)	0 / 10 (0.00%)
occurrences (all)	2	11	0
Rash			
subjects affected / exposed	6 / 10 (60.00%)	44 / 70 (62.86%)	4 / 10 (40.00%)
occurrences (all)	14	135	16
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 10 (0.00%)	9 / 70 (12.86%)	1 / 10 (10.00%)
occurrences (all)	0	12	1
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	4 / 70 (5.71%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	6 / 70 (8.57%)	2 / 10 (20.00%)
occurrences (all)	1	7	2
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Genital candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 70 (2.86%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Infection			
subjects affected / exposed	0 / 10 (0.00%)	6 / 70 (8.57%)	1 / 10 (10.00%)
occurrences (all)	0	8	1
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			

subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Tracheitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	8 / 70 (11.43%)	1 / 10 (10.00%)
occurrences (all)	1	9	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 10 (20.00%)	22 / 70 (31.43%)	3 / 10 (30.00%)
occurrences (all)	2	35	3
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	5 / 70 (7.14%)	1 / 10 (10.00%)
occurrences (all)	0	8	1
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 70 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 70 (4.29%)	1 / 10 (10.00%)
occurrences (all)	0	4	8
Hypoglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 70 (1.43%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	4 / 70 (5.71%)	2 / 10 (20.00%)
occurrences (all)	0	9	5
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	15 / 70 (21.43%)	4 / 10 (40.00%)
occurrences (all)	1	23	13
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 70 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Vitamin K deficiency subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	1 / 10 (10.00%) 1
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2011	<p>Amendment 1 included new data from preclinical and clinical trials and revised the informed consent form for genetic testing due to regulatory requirements / requests. In addition, inconsistencies and errors were corrected, and clarifications to the original protocol were made. In Amendment 1, the protocol was:</p> <ol style="list-style-type: none">1. Revised to indicate that drug-drug interactions with substrates of CYP2C8 cannot be ruled out. Caution was recommended when considering or administering medications that are metabolized by cytochrome enzyme CYP2C8 (eg, repaglinide and torsemide). Such concomitant medications were to be avoided, if possible.2. Revised to include additions of two new exclusion criteria: to exclude patients with history or current retinal vein occlusion or retinopathy; or retinal pathology considered a risk factor for these conditions. This change was made to be consistent with exclusion criteria in other MEK-inhibitor studies.3. Revised to indicate that both gemcitabine and refametinib seem to have a largely non-overlapping adverse event (AE) profile. An additional recommendation was given regarding the necessity for careful observation of the intensity and frequency of AEs (side effects) as well as the occurrence of new and unexpected AEs for the combination of the drugs administered to the patients.4. Revised to add a separate genetic informed consent. Also, a baseline blood plasma sample for mutational analysis is not to be collected from patients who reside in countries that require a separate genetic consent form, and fail to provide genetic consent.5. Revised to add a new table regarding dose adjustments and treatment interruptions triggered by transaminase elevations.
26 April 2012	<p>Amendment 2 introduced a more intensive treatment for skin toxicity, added Creatine phosphokinase (CPK) examinations to the chemistry panel, removed Cycle 1 Day 50 and Cycle 2 Day 22 from the schedule of examinations and clarified ophthalmologic examinations, exclusion criteria and echocardiography assessments. In addition, inconsistencies and errors were corrected and clarifications were made. In Amendment 2, the protocol was:</p> <ol style="list-style-type: none">1. Revised to include the application of systemic antibiotics for skin toxicity CTCAE Grade 1.2. Revised to add CPK examination to the chemistry panel, scheduled to be performed at screening, weekly within the first 4 weeks, afterwards every 2 weeks. Closer evaluations in case of CTCAE Grade 3 elevations were required. Dose modifications were required in case of CPK increase greater than or equal to (\geq) CTCAE Grade 3 for refametinib.3. Revised to include CPK increase $>$ CTCAE Grade 3 as adverse event of special interest.4. Revised to reduce the number of visits on days patients do not require a full in-hospital visit (Cycle 1 Day 50 and Cycle 2 Day 22).5. Revised to change the day of ophthalmologic examination to within 8 days (+/-) from Cycle 1 Day 43.6. Revised to extend the time required for adequate contraception from 3 months to 6 months after last study treatment.7. Revised to specify that echocardiography assessments should be performed by an experienced qualified technician or cardiologist and should be evaluated by an experienced cardiologist. The expression experienced "investigator" is not correct.

13 May 2013	<p>Amendment 3 reduced the number of efficacy and safety measurements performed after the primary completion date.</p> <ol style="list-style-type: none"> 1. Reduced the frequency of tumor assessments from every 8 weeks to every 12 weeks. 2. Specified that beyond the cut-off date for the final analysis, safety data (AEs of CTCAE Grades 3 and 4 and Serious AEs) for each patient continuing on study drug would be captured until 30 days after the individual patient had stopped study treatment. 3. Eliminated the need to (1) collect diary and records of pain medication taken before patient's visit to study site, and (2) collect blood plasma samples for end of treatment analysis for determination of the apoptosis marker cleaved cytokeratin 18 (CK18) "M30" and possibly other biomarkers of tumor response, after Amendment 3 became effective.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

'99999' in the posting indicates that data were not calculated. Decimal places were automatically truncated if last decimal equals zero.
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Notes: