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

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

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

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 13 July 2016 |
| First version publication date | 13 July 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BAY86-9766/16553 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01915589 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Bayer HealthCare AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany, |
| 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 | 08 October 2014 |
| Is this the analysis of the primary completion data? | No |

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

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 6 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Refametinib (BAY86-9766) |

Arm description:

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

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

Dosage and administration details:

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

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

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

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Refametinib (BAY86-9766) |

Reporting group description:

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

| Reporting group values | Refametinib (BAY86-9766) | Total | |
|---|---|---|---|
| Number of subjects | 16 | 16 | |
| Age Categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>65.8<br>± 12.3 | <br><br><br>- | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 13 | 13 | |
| Race<br>Units: Subjects | | | |
| White | 9 | 9 | |
| Asian | 7 | 7 | |
| Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| ECOG was measured in a scale of 0-5, where 0= Fully active, able to carry on all pre-disease performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed or chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care. Totally confined to bed or chair and, 5= Death. | | | |
| Units: Subjects | | | |
| Fully Active | 7 | 7 | |
| Restricted Active | 9 | 9 | |
| Barcelona Clinic Liver Cancer (BCLC) stage | | | |
| Barcelona Clinic Liver Cancer (BCLC) | | | |
| Units: Subjects | | | |
| B (Intermediate Stage) | 2 | 2 | |
| C (Avanced Stage) | 14 | 14 | |
| Child Pugh Classification A<br>Units: Subjects | | | |
| Child Pugh Classification A | 16 | 16 | |

## End points

### End points reporting groups

| Reporting group title | Refametinib (BAY86-9766) |
|---|---|

Reporting group description:

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

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

Subject analysis set description:

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

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

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

End point description:

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

End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were planned to report, Inferential statistics were not analysed for this endpoint.

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

Notes:

[2] - FAS

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[3] - FAS

### Statistical analyses

No statistical analyses for this end point

## Secondary: Objective Response Rate (ORR) Assessed by Investigator

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

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

Notes:

[4] - FAS

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[5] - FAS

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:
[6] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tumor Response Assessed by Central Radiological Review and Investigator

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

| | | | | |
|---|---|---|---|---|
| Investigator - RECIST: Missing | 25 (7.27 to 52.38) | | | |

Notes:

[7] - FAS

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[8] - FAS

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[9] - SAF

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response

| End point title | Duration of Response |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[10] - No objective responses were observed.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Objective Response

| End point title | Time to Objective Response |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

[11] - No objective responses were observed.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Patient Reported Outcomes (PRO)

| End point title | Patient Reported Outcomes (PRO) |
|---|---|

End point description:

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

| End point type | Other pre-specified |
|---|---|

End point timeframe:

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

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

Notes:

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

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Pharmacokinetic Analysis

| End point title | Pharmacokinetic Analysis |
|---|---|

End point description:

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

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Cycle 1, Day 15

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

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

Reporting group description:

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

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

| | | | |
|---|---|---|---|
| site conditions - Other, specify | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| CPK increased | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Heart failure | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infections and infestations - Other, specify | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Refametinib (BAY86-9766), 50 mg twice daily, Phase II | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 16 (93.75%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |

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

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

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

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

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

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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

Notes: