



## Clinical trial results:

**A phase 2, randomized, open label study to evaluate the efficacy, safety, pharmacodynamics, pharmacokinetics of the anti-ALK-1 MAB PF-03446962 in combination with best supportive care vs. best supportive care alone in adult patients with advanced hepatocellular carcinoma.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-001426-26 |
| Trial protocol           | IT ES          |
| Global end of trial date | 09 July 2014   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 25 May 2016  |
| First version publication date | 21 June 2015 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A8471005 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01911273 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Pfizer Inc.  |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, 10017  |
| Public contact               | ClinicalTrials.gov Call Centre, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | ClinicalTrials.gov Call Centre, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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:

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**Results analysis stage**

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|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 09 July 2014 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 09 July 2014 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 09 July 2014 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine whether overall survival (OS) of PF-03446962 plus best supportive care (BSC) is superior to OS of BSC in subjects with advanced HCC following sorafenib failure.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization [ICH] 1996), and the Declaration of Helsinki (World Medical Association, 1996 & 2008 versions).

In addition, the study was conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

|   |                     |
|---|---------------------|
| Actual start date of recruitment                          | 06 September 2013   |
| Long term follow-up planned                               | Yes                 |
| Long term follow-up rationale                             | Scientific research |
| Long term follow-up duration                              | 2 Years             |
| Independent data monitoring committee (IDMC) involvement? | No                  |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |          |
|--------------------------------------|----------|
| Country: Number of subjects enrolled | Japan: 3 |
| Worldwide total number of subjects   | 3        |
| EEA total number of subjects         | 0        |

Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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) | 3 |
| From 65 to 84 years  | 0 |
| 85 years and over    | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Only 3 subjects were randomized under the open-label study design: 1 subject in Arm A (PF-03446962 plus BSC) and 2 in Arm B (BSC alone). The 2 subjects randomized to Arm B (BSC alone) withdrew the consent after being aware of the assigned arm.

### Period 1

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

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | PF-03446962 plus BSC |

Arm description:

PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.

|  |                                 |
|--|---------------------------------|
| Arm type                               | Active comparator               |
| Investigational medicinal product name | PF-03446962                     |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

PF-03446962 7 mg/kg was administered IV as 1-hour infusion q2w plus BSC.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | BSC alone |
|------------------|-----------|

Arm description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

|   |                      |
|---|----------------------|
| Arm type  | best supportive care |
| No investigational medicinal product assigned in this arm |                      |

| Number of subjects in period 1     | PF-03446962 plus BSC | BSC alone |
|------------------------------------|----------------------|-----------|
| Started                            | 1                    | 2         |
| Premature termination of the study | 0                    | 0         |
| Completed                          | 0                    | 0         |
| Not completed                      | 1                    | 2         |
| Premature termination of the study | 1                    | -         |
| Consent withdrawn by subject       | -                    | 2         |



## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | PF-03446962 plus BSC |
|-----------------------|----------------------|

Reporting group description:

PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.

|                       |           |
|-----------------------|-----------|
| Reporting group title | BSC alone |
|-----------------------|-----------|

Reporting group description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

| Reporting group values                             | PF-03446962 plus BSC | BSC alone | Total |
|--|----------------------|-----------|-------|
| Number of subjects                                 | 1                    | 2         | 3     |
| Age categorical                                    |                      |           |       |
| Units: Subjects                                    |                      |           |       |
| In utero   | 0                    | 0         | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                    | 0         | 0     |
| Newborns (0-27 days)                               | 0                    | 0         | 0     |
| Infants and toddlers (28 days-23 months)           | 0                    | 0         | 0     |
| Children (2-11 years)                              | 0                    | 0         | 0     |
| Adolescents (12-17 years)                          | 0                    | 0         | 0     |
| Adults (18-64 years)                               | 1                    | 2         | 3     |
| From 65-84 years                                   | 0                    | 0         | 0     |
| 85 years and over                                  | 0                    | 0         | 0     |
| Gender categorical                                 |                      |           |       |
| Units: Subjects                                    |                      |           |       |
| Female   | 1                    | 0         | 1     |
| Male   | 0                    | 2         | 2     |

## End points

### End points reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | PF-03446962 plus BSC |
| Reporting group description:<br>PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.  |                      |
| Reporting group title  | BSC alone            |
| Reporting group description:<br>BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life. |                      |

### Primary: Overall Survival (OS)

|  |                                      |
|--|--------------------------------------|
| End point title  | Overall Survival (OS) <sup>[1]</sup> |
| End point description:<br>OS was the duration from date of randomization to date of death due to any cause. For subjects who are alive, overall survival was censored at the last contact. Death was determined from adverse event (AE) data where outcome was death or from follow-up contact data where the subject current status was death.<br>Analysis population description: Full analysis set (FAS) included all randomized subjects regardless of what treatment, if any, was received. |                                      |
| End point type   | Primary                              |
| End point timeframe:<br>From first randomization to date of death from any cause, whichever came first, assessed up to 24 months after last subject randomization.   |                                      |

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: Insufficient data available to conduct adequate analysis due to premature termination of the study.

| End point values                 | PF-03446962 plus BSC   | BSC alone              |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 1 <sup>[2]</sup>       | 2 <sup>[3]</sup>       |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

Notes:

[2] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[3] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Tumor Progression (TTP)

|  |                                 |
|--|---------------------------------|
| End point title  | Time to Tumor Progression (TTP) |
| End point description:<br>TTP was defined as the time from first randomization to date of first documentation of objective tumor progression. If tumor progression data included more than (>) 1 date, the first date was to be used. TTP (in months) was calculated as first event date or last known progression-free date minus the first |                                 |

randomization date plus 1 divided by 30.4. Tumor progression was determined from oncologic assessment data (where data meet the criteria for progressive disease per Responses Evaluation Criteria in Solid Tumors [RECIST]).

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization. |           |

|                                  |                        |                        |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| <b>End point values</b>          | PF-03446962 plus BSC   | BSC alone              |  |  |
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 1 <sup>[4]</sup>       | 2 <sup>[5]</sup>       |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

Notes:

[4] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[5] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-Free Survival (PFS)

|   |                                 |
|---|---------------------------------|
| End point title   | Progression-Free Survival (PFS) |
| End point description:  |                                 |
| PFS was defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included >1 date, the first date was to be used. PFS (in months) was calculated as first event date minus first randomization date plus 1 divided by 30.4. |                                 |
| Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.   |                                 |
| End point type  | Secondary                       |
| End point timeframe:  |                                 |
| Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization.   |                                 |

|                                  |                        |                        |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| <b>End point values</b>          | PF-03446962 plus BSC   | BSC alone              |  |  |
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 1 <sup>[6]</sup>       | 2 <sup>[7]</sup>       |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

Notes:

[6] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[7] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

## Statistical analyses



**Secondary: Objective Response Rate (ORR) - Percentage of Participants With Objective Response**

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) - Percentage of Participants With Objective Response |
|-----------------|--|

## End point description:

ORR was defined as the proportion of participants with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1, relative to all randomized participants. CR were those that persisted on repeat imaging study more than or equal to ( $\geq$ ) 4 weeks after initial documentation of response. PR was defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions. Participants who did not have on study radiographic tumor re-evaluation or who died, progressed or dropped out for any reason prior to reaching a CR or PR were to be counted as non-responders in the assessment of ORR. A participant who initially met the criteria for a PR and then subsequently became a confirmed CR, was to be assigned a best response of CR.

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

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

## End point timeframe:

Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization.

| End point values                 | PF-03446962 plus BSC   | BSC alone              |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 1 <sup>[8]</sup>       | 2 <sup>[9]</sup>       |  |  |
| Units: Percentage of Subjects    |                        |                        |  |  |
| number (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

## Notes:

[8] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[9] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of Response (DR)**

|                 |                           |
|-----------------|---------------------------|
| End point title | Duration of Response (DR) |
|-----------------|---------------------------|

## End point description:

DR was defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included  $>1$  date, the first date was to be used. DR (in months) was calculated as the end date for DR minus date of first CR or PR that was subsequently confirmed plus 1 divided by 30.4. CR was defined as disappearance of all target lesions and non-target, if any. PR was defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions. Analysis population description: Subgroup of subjects with objective response. Since objective response was not assessed in any of the subjects, ideally the number of subjects analyzed field should be 0 and the reason was insufficient data available to conduct adequate analysis due to premature termination of the study.

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

## End point timeframe:

From first randomization to date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months after last subject randomization

| End point values                 | PF-03446962 plus BSC | BSC alone         |  |  |
|----------------------------------|----------------------|-------------------|--|--|
| Subject group type               | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed      | 0 <sup>[10]</sup>    | 0 <sup>[11]</sup> |  |  |
| Units: Months                    |                      |                   |  |  |
| median (confidence interval 95%) | ( to )               | ( to )            |  |  |

Notes:

[10] - No data displayed because Outcome Measure has zero total subjects analyzed.

[11] - No data displayed because Outcome Measure has zero total subjects analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Disease Control Rate (DCR) at 16 Weeks

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with Disease Control Rate (DCR) at 16 Weeks |
|-----------------|--|

End point description:

DCR was defined as the proportion of subjects with confirmed CR or confirmed PR or a best response of stable disease (SD)  $\geq 16$  weeks according to RECIST, relative to all randomized subjects. CR was defined as disappearance of all target lesions. PR was defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study.

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

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

End point timeframe:

From first randomization to date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months after last participant randomization.

| End point values                  | PF-03446962 plus BSC   | BSC alone              |  |  |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type                | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed       | 1 <sup>[12]</sup>      | 2 <sup>[13]</sup>      |  |  |
| Units: Percentage of Participants |                        |                        |  |  |
| number (confidence interval 95%)  | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

Notes:

[12] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[13] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep)

|   |  |
|---|--|
| End point title   | Change From Baseline in Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep) |
| End point description:  |  |
| <p>Patient reported outcomes (PROs) were assessed using the FACT-Hep. The FACT-Hep included the FACT-general (FACT-G) and a hepatobiliary module, it consisted of the 27-item FACT-G, which assessed generic health-related quality of life (HRQoL) concerns, and the 18-item hepatobiliary subscale (HS), which assessed disease-specific issues. The questionnaire used a 5 point Likert scale from '0' "not at all" to '4' "very much" regarding how much each item was present in the last 7 days; lower score indicated severer symptom. Eight of the items (lack of energy, pain, weight loss, back pain, fatigue, stomach pain/discomfort, nausea, and jaundice) made up the Fact Hepatobiliary Symptom Index (FHSI 8) were considered to be symptoms specific to hepatobiliary cancer.</p> <p>Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.</p> |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Screening, Cycle 1 Day1,8; Cycle >=2 Day 1; End of treatment, survival follow-up up to 24 months after last subject randomization.  |  |

|                               |                      |                   |  |  |
|-------------------------------|----------------------|-------------------|--|--|
| <b>End point values</b>       | PF-03446962 plus BSC | BSC alone         |  |  |
| Subject group type            | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed   | 1 <sup>[14]</sup>    | 2 <sup>[15]</sup> |  |  |
| Units: Unites on Scale        |                      |                   |  |  |
| log mean (standard deviation) | 99999 (± 99999)      | 99999 (± 99999)   |  |  |

Notes:

[14] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[15] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum PF-03446962 Serum Concentration (Cmax)

|   |  |
|---|--|
| End point title   | Maximum PF-03446962 Serum Concentration (Cmax) |
| End point description:  |  |
| Analysis population description: The pharmacokinetic (PK) concentration set consisted of all subjects who were treated and had at least one concentration on at least 1 day of PK assessment. |  |
| End point type  | Secondary                                      |
| End point timeframe:  |  |
| 1 hour (after start of infusion) on Day1 of Cycles 1, 2, 4, 6, and 8  |  |

|  |                      |                   |  |  |
|--|----------------------|-------------------|--|--|
| <b>End point values</b>                  | PF-03446962 plus BSC | BSC alone         |  |  |
| Subject group type                       | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed              | 1 <sup>[16]</sup>    | 0 <sup>[17]</sup> |  |  |
| Units: microgram per milliliter (mcg/mL) |                      |                   |  |  |
| geometric mean (standard deviation)      | 99999 (± 99999)      | ( )               |  |  |

Notes:

[16] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[17] - No specimen were analyzed

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trough Serum Concentration of PF-03446962 (Ctrough)

|                 |   |
|-----------------|---|
| End point title | Trough Serum Concentration of PF-03446962 (Ctrough) |
|-----------------|---|

End point description:

Analysis population description: The PK concentration set consisted of all subjects who were treated and had at least one concentration on at least 1 day of PK assessment.

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

End point timeframe:

0 hour (predose) on Day 1 of Cycles 1, 2, 4, 6, and 8

| End point values                    | PF-03446962 plus BSC | BSC alone         |  |  |
|-------------------------------------|----------------------|-------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed         | 1 <sup>[18]</sup>    | 0 <sup>[19]</sup> |  |  |
| Units: mcg/mL                       |                      |                   |  |  |
| geometric mean (standard deviation) | 99999 (± 99999)      | ( )               |  |  |

Notes:

[18] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[19] - No specimen were analyzed

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Human Anti-Human Antibodies (HAHA)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with Human Anti-Human Antibodies (HAHA) |
|-----------------|--|

End point description:

Analysis population description: The immunogenicity assessment consisted of all subjects who had at least 1 sample on at least 1 day of immunogenicity assessment.

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

End point timeframe:

Cycle 1, 2, 4, 6, 8 Day 1 at 0 hour (pre-dose)

|                             |                      |                   |  |  |
|-----------------------------|----------------------|-------------------|--|--|
| <b>End point values</b>     | PF-03446962 plus BSC | BSC alone         |  |  |
| Subject group type          | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed | 1 <sup>[20]</sup>    | 0 <sup>[21]</sup> |  |  |
| Units: Subjects             |                      |                   |  |  |
| number (not applicable)     | 99999                |                   |  |  |

Notes:

[20] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[21] - No specimen were analyzed

## Statistical analyses

No statistical analyses for this end point

## Secondary: Presence of Sensitivity Signature

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Presence of Sensitivity Signature |
|-----------------|-----------------------------------|

End point description:

Tumor molecular characteristics including but not limited to transcriptomic (RNA) signatures of sensitivity.

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

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

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawal.

|                             |                      |                   |  |  |
|-----------------------------|----------------------|-------------------|--|--|
| <b>End point values</b>     | PF-03446962 plus BSC | BSC alone         |  |  |
| Subject group type          | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed | 0 <sup>[22]</sup>    | 0 <sup>[23]</sup> |  |  |
| Units: Percentage           |                      |                   |  |  |
| number (not applicable)     |                      |                   |  |  |

Notes:

[22] - No data displayed because Outcome Measure has zero total subjects analyzed.

[23] - No data displayed because Outcome Measure has zero total subjects analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Ratio to Baseline of Serum Circulating Protein Concentration

|                 |  |
|-----------------|--|
| End point title | Ratio to Baseline of Serum Circulating Protein Concentration |
|-----------------|--|

End point description:

Protein involved TGFB1, VEGF-A, VEGF-C, PIGF, Endoglin, BMP-9, VEGFR1, VEGFR2, VEGFr3, Ang-2, VEGF-D, CD54, CD106, and CCL2. Tumor molecular characteristics including but not limited to transcriptomic (ribonucleic acid) signatures of efficacy.

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

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

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawal.

| End point values            | PF-03446962 plus BSC | BSC alone         |  |  |
|-----------------------------|----------------------|-------------------|--|--|
| Subject group type          | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed | 1 <sup>[24]</sup>    | 0 <sup>[25]</sup> |  |  |
| Units: Percentage           |                      |                   |  |  |
| number (not applicable)     | 99999                |                   |  |  |

Notes:

[24] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[25] - No data displayed because Outcome Measure has zero total subjects analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Observed Serum Concentration of Circulating Protein

|                 |   |
|-----------------|---|
| End point title | Observed Serum Concentration of Circulating Protein |
|-----------------|---|

End point description:

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

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

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawal.

| End point values            | PF-03446962 plus BSC | BSC alone         |  |  |
|-----------------------------|----------------------|-------------------|--|--|
| Subject group type          | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed | 1 <sup>[26]</sup>    | 0 <sup>[27]</sup> |  |  |
| Units: mcg/mL               |                      |                   |  |  |
| number (not applicable)     | 99999                |                   |  |  |

Notes:

[26] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[27] - No data displayed because Outcome Measure has zero total subjects analyzed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 28 days after the last administration of study medication.

Adverse event reporting additional description:

Three subjects were assigned to receive study treatment, as of study termination date. One subject was assigned to receive PF-03446962 plus BSC treatment and discontinued due to progression of disease; 2 were assigned to receive BSC only treatment and discontinued due to withdrawal of consent.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | PF-03446962 plus BSC |
|-----------------------|----------------------|

Reporting group description:

PF-03446962 7 mg/kg was administered IV as 1-hour infusion q2w plus BSC.

|                       |           |
|-----------------------|-----------|
| Reporting group title | BSC alone |
|-----------------------|-----------|

Reporting group description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

| Serious adverse events                            | PF-03446962 plus BSC | BSC alone     |  |
|---|----------------------|---------------|--|
| Total subjects affected by serious adverse events |                      |               |  |
| subjects affected / exposed                       | 0 / 1 (0.00%)        | 0 / 2 (0.00%) |  |
| number of deaths (all causes)                     | 0                    | 0             |  |
| number of deaths resulting from adverse events    | 0                    | 0             |  |

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

| Non-serious adverse events                            | PF-03446962 plus BSC | BSC alone     |  |
|---|----------------------|---------------|--|
| Total subjects affected by non-serious adverse events |                      |               |  |
| subjects affected / exposed                           | 1 / 1 (100.00%)      | 0 / 2 (0.00%) |  |
| Respiratory, thoracic and mediastinal disorders       |                      |               |  |
| Oropharyngeal pain                                    |                      |               |  |
| subjects affected / exposed                           | 1 / 1 (100.00%)      | 0 / 2 (0.00%) |  |
| occurrences (all)                                     | 2                    | 0             |  |
| Infections and infestations                           |                      |               |  |

|                             |                 |               |  |
|-----------------------------|-----------------|---------------|--|
| Gastroenteritis             |                 |               |  |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 2 (0.00%) |  |
| occurrences (all)           | 1               | 0             |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 26 August 2013   | <p>1) Section 5.2.5, Dose Reductions: Table 2, "PF 03446962 Dose Modification at Start of Subsequent Cycle" updated to reflect the most common type of toxicities associated with the administration of PF 03446962.</p> <p>2) In agreement with updated Table 2, amylase and lipase have been added to Appendix 2, List of Laboratory Tests.</p> <p>3) Schedule of Activities: time of collection of Banked Biospecimens, Blood Sample for Soluble Proteins and HAHA corrected.</p>   |
| 04 November 2013 | <p>1) The description of the safety profile of PF 0344962 has been expanded and updated in agreement with the current IB.</p> <p>2) Some study secondary objectives have been expanded in order to clarify the translational research component of the study. The relevant study endpoints have also been clarified.</p> <p>3) In order to limit patient burden and to support the identification of mechanism of resistance to PF 0344962, mandatory tumor biopsy collection at the time of disease progression has been limited to those patients randomized to PF 0344962 (Arm A) who progress after showing objective response or stable disease for at least 16 weeks after randomization.</p> <p>4) The duration of treatment/active observation periods have been clarified in the study design section.</p> <p>5) Some patient selection criteria have been clarified. Patients with known portal hypertension and untreated high risk esophageal varices have been excluded. Patients with history of any other malignancy in the previous 3 years have also been excluded.</p> <p>6) Dose Modification Criteria for PF 03446962 have been clarified.</p> <p>7) Schedule of Activities: inconsistencies between table and footnotes and some protocol sections have been fixed. Some footnotes have been reworded to improve clarity. IRC description has been added.</p> <p>8) PRO testing on Day 8 of Cycle 1 has been added to Arm B.</p> <p>9) EoT in non Member States has been defined.</p> <p>10) Appendix 2 List of Laboratory Tests has been clarified.</p> <p>11) Appendix 4 List of abbreviations and definitions of terms has been added.</p> <p>12) Typos and minor inconsistencies have been fixed across the protocol.</p> |
| 08 April 2014    | <p>1) The study design has been changed from open label to double blind in order to minimize the risk of premature dropout from the comparator arm and preserve the integrity of the study.</p> <p>2) Schedule of Activities and assessment types and frequencies have been made identical in both treatment arms.</p> <p>3) A statement relevant to failure of targeted agents to show clinical benefit in the 2nd line treatment of HCC has been included upon IRB/health authority request.</p> <p>4) Timing of adverse events and laboratory abnormalities occurrence has been removed from relevant secondary endpoints since it is not part of the standard safety analysis.</p> <p>5) Reference to the pathology report and statement has been removed from the protocol with details included in the Study Manual.</p> <p>6) The description of the Internal Review Committee role has been elaborated.</p> <p>7) Editorial changes to address typos and align protocol language with updated protocol template have been made.</p>  |

Notes:

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## **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.

|  |
|--|
| This study was prematurely terminated due to a Sponsor decision not to pursue the clinical development of PF-03446962 as monotherapy in second-line HCC. Primary and secondary objectives were not achieved in this study due to the premature termination |
|--|

Notes: