Clinical trial results:
A PHASE II TRIAL OF PF-04856884 (CVX-060), A SELECTIVE ANGIOPOIETIN-2 (ANG-2) INHIBITOR IN COMBINATION WITH AG-013736 (AXITINIB) IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC RENAL CELL CARCINOMA

Summary

EudraCT number	2011-002190-33
Trial protocol	ES IT CZ DE GB AT FI
Global end of trial date	27 March 2014

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	B1131004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01441414
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, , United States, NY 10017
Public contact	Clinical Trials.gov Call Center, Pfizer Inc., 001 800 7181021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc., 001 800 7181021, ClinicalTrials.govCallCenter@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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part I: To confirm that the combination of PF-04856884 and AG-013736 is safe and tolerable at the doses to be used in Part II of the study.
Part II: To document clinical activity of the combination of PF-04856884 and AG-013736 or AG-013736 alone as measured by PFS in adult
patients with previously treated Metastatic Renal Cell Cancer (mRCC).

Protection of trial subjects:

Palliative and supportive care for disease related symptoms was available per local standard of care for all patients on this study. Low dose oral steroids (defined as <5 mg per day prednisone or equivalent), short course of oral steroids (defined as <5 consecutive days of therapy) or topical or inhaled steroids at any dose may have been taken during the study. No other chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications were permitted while the patient was on study; patients on luteinizing hormone releasing hormone (LHRH) analogs may have been maintained on treatment. Any disease progression requiring other forms of specific anticancer therapy were cause for discontinuation from study drug.

Background therapy:

- Part I: Have received 1 3 prior systemic regimens for treatment of mRCC.
- Part II: Evidence of disease progression following 1 prior regimen administered as 1st line therapy for mRCC. The prior regimen must have contained one of the following:
- VEGFR 2 TKI such as (but not limited to) pazopanib, sunitinib, tivozanib, or sorafenib;
- Other anti VEGF compounds, such as bevacizumab.

As of 06 November 2012, based upon the safety findings from Part I of the study, Pfizer decided not to open patient enrolment onto Part II of the study.

Evidence for comparator: -

Actual start date of recruitment	21 October 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	Czech Republic: 1
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	18
EEA total number of subjects	1

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)	10
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter, open-label study consisted of a safety lead in stage (Part I) followed by a randomized Phase 2 stage (Part II). A total of 18
participants were screened and assigned to treatment in Part I, with 3 participants completing Part I of the study. At the completion of Part I, all 18 participants had discontinued combined treatment.

Pre-assignment

Screening details:

During Part I, 3 to 4 participants were initially treated with the study drug combination in 28-day cycles. If no participants experienced Cycle 1 dose limiting toxicities (DLTs), another 6 to 9 participants were treated at this dose level. Part II of the study was to be initiated if Cycle 1 DLTs were observed in <33% in at least 12 participants.

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	PF-04856884 + AG-013736 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	PF-04856884 + AG-013736

Arm description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

Arm type	Experimental
Investigational medicinal product name	PF 04856884 and AG 013736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion, Tablet
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Study treatment began within 3 days of registering the patient for Part I.
PF 04856884: During Cycle 1, this was given as a 60 minute infusion. After the first cycle, the infusion duration was reduced to 30 minutes for all subsequent cycles. AG 013736: This was taken orally with or without food. Twice daily doses were approximately 12 hours apart and at approximately the same times each day. For patients enrolled in Part I, the morning dose coincided with the timing of the start of the infusion at all visits with post dose sampling.
Patients in Part I received PF 04856884 15 mg/kg/week and AG 013736 5 mg BID. Following the decision of 06 November 2012, any patient remaining in Part I continued to receive PF 04856884 at a reduced dose of 10 mg/kg/week in combination with AG 013736 (5 mg BID) or AG 013736 alone (5 mg BID).

Number of subjects in period 1	PF-04856884 + AG-013736
Started	18
Completed	3
Not completed	15
Participant died	9
Study terminated by sponsor	2
Other reasons	3
Participant refused further follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	PF-04856884 + AG-013736

Reporting group description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

Reporting group values	PF-04856884 + AG-013736	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
< 18	0	0	
18-44	2	2	
45-64	8	8	
65 years and over	8	8	
Age continuous Units: years			
arithmetic mean	63.2		
standard deviation	± 10.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	14	14	

End points

End points reporting groups

Reporting group title	PF-04856884 + AG-013736

Reporting group description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

Subject analysis set title	All-causality CTCAE Grade 3
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of all-causality CTCAE Grade 3 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	All-causality CTCAE Grade 4
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of all-causality CTCAE Grade 4 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	All-causality CTCAE Grade 5
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of all-causality CTCAE Grade 5 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	Treatment-related CTCAE Grade 3
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of treatment-related CTCAE Grade 3 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	Treatment-related CTCAE Grade 4
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of treatment-related CTCAE Grade 4 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	Treatment related CTCAE Grade 5
Subject analysis set type	Full analysis

Subject analysis set description:

Incidence and severity of all-causality CTCAE Grade 5 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category.

Subject analysis set title	All-causality CTCAE Grade 2
Subject analysis set type	Full analysis

Subject analysis set description:

Number of participants who had serious TEAEs (all-causality) of CTCAE Grade 2 TEAEs are presented

Primary: Number of Participants With non-serious Adverse Events (AEs) in Part I (Reported in ≥2 of the participants)

End point title	Number of Participants With non-serious Adverse Events (AEs) in Part I (Reported in ≥2 of the participants)[1]

End point description:

Incidence and severity of all treatment-emergent AEs (TEAEs) of both all-causality and treatment-related are presented by preferred term (PT) categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades reported in ≥2 participants (for any PT). Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week)

or AG-013736 alone (5 mg twice a week). Where a TEAE-PT is already included under all-causality TEAEs, the treatment-related TEAE-PTs are presented as "0"; and where less than 2 participants experienced treatment-related TEAE, the data is presented as "0" in the following table.

End point type	Primary

End point timeframe:

4 months

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: Statistical analysis was not required by the statistical analysis plan (SAP) for this endpoint.

End point values	All-causality CTCAE Grade 3	All-causality CTCAE Grade 4	All-causality CTCAE Grade 5	Treatment-related CTCAE Grade 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	18	18	18
Units: participants				
Anaemia	0	0	0	0
Leukocytosis	2	0	0	0
Pericardial effusion	0	1	0	0
Hyperthyroidism	0	0	0	0
Hypothyroidism	0	0	0	0
Vision blurred	0	0	0	0
Abdominal pain	1	0	0	0
Constipation	0	0	0	0
Diarrhoea	0	0	0	0
Dry mouth	0	0	0	0
Gastritis	0	0	0	0
Nausea	1	0	0	1
Oral pain	0	0	0	0
Stomatitis	0	0	0	0
Toothache	0	0	0	0
Vomiting	1	0	0	1
Asthenia	1	0	0	1
Fatigue	5	0	0	4
Oedema peripheral	0	0	0	0
Pneumonia	1	0	0	0
Upper respiratory tract infection	0	0	0	0
Urinary tract infection	1	0	0	0
Blood creatinine increased	0	0	0	0
Weight decreased	2	0	0	1
Decreased appetite	1	0	0	1
Dehydration	0	0	0	0
Hypercalcaemia	0	0	0	0
Hypokalaemia	1	0	0	0
Hyponatraemia	1	0	0	0
Hypovolaemia	0	0	0	0
Arthralgia	1	0	0	0
Back pain	1	0	0	0
Muscle spasms	0	0	0	0
Muscular weakness	0	0	0	0
Myalgia	0	0	0	0
Cerebrovascular accident	1	1	0	1

Dizziness	0	0	0	0
Headache	1	0	0	1
Migraine	1	0	0	1
Neuropathy peripheral	1	0	0	0
Depression	1	0	0	0
Insomnia	1	0	0	1
Proteinuria	0	0	0	0
Cough	0	0	0	0
Dysphonia	0	0	0	0
Dyspnoea	1	0	0	0
Hypoxia	1	0	0	0
Pleural effusion	1	0	0	0
Pulmonary embolism	1	1	0	1
Night sweats	0	0	0	0
Palmar-plantar erythrodysaesthesia	0	0	0	0
Hot flush	0	0	0	0
Hypertension	5	0	0	4
Hypotension	1	0	0	0

End point values	Treatment-related CTCAE Grade 4	Treatment related CTCAE Grade 5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: participants				
Anaemia	0	0		
Leukocytosis	0	0		
Pericardial effusion	1	0		
Hyperthyroidism	0	0		
Hypothyroidism	0	0		
Vision blurred	0	0		
Abdominal pain	0	0		
Constipation	0	0		
Diarrhoea	0	0		
Dry mouth	0	0		
Gastritis	0	0		
Nausea	0	0		
Oral pain	0	0		
Stomatitis	0	0		
Toothache	0	0		
Vomiting	0	0		
Asthenia	0	0		
Fatigue	0	0		
Oedema peripheral	0	0		
Pneumonia	0	0		
Upper respiratory tract infection	0	0		
Urinary tract infection	0	0		
Blood creatinine increased	0	0		
Weight decreased	0	0		
Decreased appetite	0	0		

Dehydration	0	0		
Hypercalcaemia	0	0		
Hypokalaemia	0	0		
Hyponatraemia	0	0		
Hypovolaemia	0	0		
Arthralgia	0	0		
Back pain	0	0		
Muscle spasms	0	0		
Muscular weakness	0	0		
Myalgia	0	0		
Cerebrovascular accident	1	0		
Dizziness	0	0		
Headache	0	0		
Migraine	0	0		
Neuropathy peripheral	0	0		
Depression	0	0		
Insomnia	0	0		
Proteinuria	0	0		
Cough	0	0		
Dysphonia	0	0		
Dyspnoea	0	0		
Hypoxia	0	0		
Pleural effusion	0	0		
Pulmonary embolism	1	0		
Night sweats	0	0		
Palmar-plantar erythrodysaesthesia	0	0		
Hot flush	0	0		
Hypertension	0	0		
Hypotension	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Serious Adverse Events (SAEs) in Part I (Reported in ≥2 participants)

End point title	Number of Participants with Serious Adverse Events (SAEs) in Part I (Reported in ≥2 participants)[2]

End point description:

Incidence and severity of all-causality serious adverse events (SAEs) are presented by PT categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades. Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week). Participants with treatment-related TEAE are coded as NA if they appear for the same preferred term under all-causality TEAE.

End point type	Primary

End point timeframe:

4 months

Notes:

[2] - 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 required by the statistical analysis plan (SAP) for this endpoint.

End point values	All-causality CTCAE Grade 3	All-causality CTCAE Grade 4	All-causality CTCAE Grade 5	All-causality CTCAE Grade 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	18	18	18
Units: participants				
Pneumonia	1	0	0	1
Pleural effusion	1	0	0	1
Ileus	0	0	0	1
Abdominal pain	1	0	0	0
Ascites	0	0	0	1
Lung infection	1	0	0	0
Back pain	1	0	0	0
Musculoskeletal chest pain	1	0	0	0
Convulsion	0	0	0	1
Embolism	0	0	0	1
Hyponatraemia	1	0	0	0
Dyspnoea	1	0	0	0
Hypotension	1	0	0	0
Cerebrovascular accident	1	1	0	0
Migraine	1	0	0	0
Meningioma	1	0	0	0
Hypovolaemia	0	0	0	1
Pulmonary embolism	1	1	0	0
Pericardial effusion	0	1	0	0
Gastrointestinal disorder	0	0	1	0
Chest discomfort	1	0	0	0
Hypertension	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) in Part II

End point title	Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) in Part II[3]

End point description:

PFS is defined as the time (in days) from date of randomization to first documentation of investigator assessed tumor progression or death, whichever comes first. Progression free survival was to be calculated as (first event date – the date of randomization +1).

End point type	Primary

End point timeframe:

3 years

Notes:

[3] - 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 required by the statistical analysis plan (SAP) for this endpoint.

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: days				

Notes:

[4] - PFS in Part II was not assessed due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with non-serious AEs and SAEs

End point title	Number of Participants with non-serious AEs and SAEs

End point description:

Incidence and severity of all-causality AEs and SAEs to be presented by PT categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades. Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

End point type	Secondary

End point timeframe:

3 years

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: participants				

Notes:

[5] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

End point title	Overall Response Rate (ORR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

End point description:

ORR is defined as the proportion of participants with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST), relative to all randomized participants as defined in the FA Set. Confirmed responses are those that persist on repeat

imaging study ≥ 4 weeks after initial documentation of response. Participants who do not have on-study radiographic tumor evaluation or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders (NR) in the assessment of ORR.

End point type	Secondary

End point timeframe:

4 months

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (not applicable)				
Complete response (CR)	0			
Partial response (PR)	11.1			
ORR (CR + PR)	11.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

End point title	Duration of Response (DR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

End point description:

DR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of tumor progression or to death due to cancer. Duration of tumor response was to be calculated as (the end date for DR − first CR or PR that is subsequently confirmed +1).

End point type	Secondary

End point timeframe:

3 years

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: weeks				

Notes:

[6] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax (Time when maximum serum PF-04856884 concentration was reached)

End point title	Tmax (Time when maximum serum PF-04856884 concentration was reached)

End point description:

Pharmacokinetic parameter, Tmax (Time when maximum serum PF-04856884 concentration was reached) was done using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hour				
arithmetic mean (standard deviation)				
CYCLE1/DAY1	2 (± 1.645)			
CYCLE1/DAY22	3 (± 2.1122)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax (observed peak serum PF-04856884 concentration)

End point title	Cmax (observed peak serum PF-04856884 concentration)

End point description:

Pharmacokinetic parameter Cmax (observed peak PF-04856884 serum concentration) was estimated using noncompartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
arithmetic mean (standard deviation)				
CYCLE1/DAY1	337100 (± 76245)			
CYCLE1/DAY22	531400 (± 154780)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin (trough PF-04856884 serum concentration)

End point title	Cmin (trough PF-04856884 serum concentration)

End point description:

Pharmacokinetic parameter Cmin (trough PF-04856884 serum concentration) was estimated using noncompartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
arithmetic mean (standard deviation)				
CYCLE1/DAY1	932.7 (± 3499.1)			
CYCLE1/DAY22	168900 (± 84507)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Anti-drug antibodies (ADA) Samples Confirmed Positive

End point title	Number of Anti-drug antibodies (ADA) Samples Confirmed Positive

End point description:

Detection of neutralizing anti-PF-04856884 antibodies was based on the ability of anti-PF-04856884 neutralizing antibodies to bind to Tag-PF-04856884.

End point type	Secondary

End point timeframe:

0 and 360 hours post dose and end of study

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ADA samples				
Number of ADA samples Analyzed	91			
Number of ADA Samples Confi	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) as measured by an Independent Radiological Assessment

End point title	Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) as measured by an Independent Radiological Assessment

End point description:

PFS is defined as the time (in days) from date of randomization to first documentation of investigator assessed tumor progression or death, whichever comes first. PFS was to be calculated as (first event date – the date of randomization +1).

End point type	Secondary

End point timeframe:

3 years

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: days				

Notes:

[7] - This endpoint of estimating median PFS was not assessed due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 2 years

End point title	Overall Survival (OS) at 2 years

End point description:

OS is defined as the time from the first dose date to date of death. For participants not expiring, their survival times will be censored at the last date they are known to be alive, or 2 year whichever is earlier. The 2-year OS rate will be estimated from a time-to event analysis of OS.

End point type	Secondary

End point timeframe:

5 years

End point values	PF-04856884 + AG-013736			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: months				

Notes:

[8] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day the first dose of the investigational product was administered up to 1 year.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one participant and as nonserious in another participant, or one participant may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	PF 04856884 + AG 013736

Reporting group description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

Serious adverse events	PF 04856884 + AG 013736		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 18 (66.67%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Hypotension				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Pericardial effusion				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migrane				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest discomfort				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				

subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Ileus				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	PF 04856884 + AG 013736		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	9 / 18 (50.00%)		
occurrences (all)	19		
Hypotension			

subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Chest pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	11 / 18 (61.11%)		
occurrences (all)	22		
Inflammation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	4		
Pyrexia			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Seasonal allergy			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Scrotal oedema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 18 (38.89%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	8		
Dyspnoea exertional			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypoxia			

subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Rhinalgia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	5		
Flat affect			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	7 / 18 (38.89%)		
occurrences (all)	7		
Restlessness			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Investigations			
Blood creatine increased			

subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Coagulation time prolonged			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Haptoglobin increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Neutrophil count abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	17		
White blood cell count abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pericardial effusion			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Sinus tachycardia			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Depressed level of consciousness			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	5		
Hypoaesthesia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Memory impairment			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	4		
Neuropathy peripheral			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Syncope			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	7		
Leukocytosis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Vitreous floaters			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Abdominal pain				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	7			
Aphthous stomatitis				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Ascites				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	7			
Constipation				
subjects affected / exposed	8 / 18 (44.44%)			
occurrences (all)	11			
Diarrhoea				
subjects affected / exposed	10 / 18 (55.56%)			
occurrences (all)	22			
Dry mouth				
subjects affected / exposed	3 / 18 (16.67%)			
occurrences (all)	3			
Eructation				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Faecal incontinence				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Glossodynia				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	11 / 18 (61.11%)			
occurrences (all)	18			

Oral pain subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Stomatitis subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Toothache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Vomiting subjects affected / exposed occurrences (all)	10 / 18 (55.56%) 24		
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Hepatic cyst subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nail disorder subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Night sweats subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Onychalgia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Pruritus			

subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Skin disorder subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 2		
Renal and urinary disorders Nocturia subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 3 / 18 (16.67%) 4 1 / 18 (5.56%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	 2 / 18 (11.11%) 2 2 / 18 (11.11%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Groin pain	 3 / 18 (16.67%) 3 5 / 18 (27.78%) 7		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	7		
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Candida infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Cystitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Peritonitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 18 (66.67%)		
occurrences (all)	26		
Dehydration			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	7		
Hypercalcaemia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Hypercholesterolaemia			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypovolaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 November 2012	PF-04856884 in combination with AG-013736 during Part I of the study showed a higher than expected frequency of arterial thrombotic events or venous thrombotic events in the 18 patients with mRCC. These specific events included pulmonary embolism in 2 patients, cerebrovascular accident in 2 patients, gastrointestinal disorder (presumed bowel ischemia) in 1 patient, and chest discomfort in 1 patient. Based on these safety concerns, Pfizer decided not to open patient enrolment onto Part II of the study. On 06 November 2012, based upon the safety findings from Part I of this study (B1131004) and due to strategic considerations, Pfizer decided not to open patient enrolment onto Part II of the study and terminated the study.	-

Notes:

Limitations and caveats

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

Since this application does not allow the character strings in the data fields, some data which is actually reported as "not reported" in the Clinical Study Report as "NOT REPORTED" have been reported as 0 in this disclosure.

Notes: