Clinical trial results:
A Randomized Phase 2 Study of PF-05212384 Plus Irinotecan Versus Cetuximab Plus Irinotecan in Patients With KRAS and NRAS Wild Type Metastatic Colorectal Cancer

Summary

EudraCT number	2013-002095-40
Trial protocol	BE IT ES
Global end of trial date	06 April 2016

Results information

Result version number	v1 (current)
This version publication date	10 February 2017
First version publication date	10 February 2017

Trial information

Trial identification

Sponsor protocol code	B2151005

Additional study identifiers

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

Notes:

Sponsors

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

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2016
Global end of trial reached?	Yes
Global end of trial date	06 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate whether PF-05212384 in combination with irinotecan was superior to cetuximab in combination with irinotecan in prolonging progression-free survival (PFS) in subjects with Kirsten ras oncogene (KRAS) and neuroblastoma ras viral oncogene homolog (NRAS) wild type mCRC who had progressed following prior treatment with irinotecan, oxaliplatin, and fluoropyrimidine.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 5
Worldwide total number of subjects	19
EEA total number of subjects	0

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)	13
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prior to study termination, a total of 20 potential subjects were screened, and 19 of them were enrolled and treated, which included 8 subjects from the United States, 6 subjects from Japan, and 5 subjects from Korea.

Pre-assignment

Screening details:

A total of 20 potential subjects were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-05212384 + Irinotecan: Arm A

Arm description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF 05212384 was only dosed on Days 9, 16 and 23. After one cycle of dosing with PF-05212384, in subsequent cycles, the dose level remained at 110 mg or was escalated based on the occurrences of dose limiting toxicities (DLTs) in previous cycle and at the discretion of the investigator. Subjects enrolled in Korea remained at the 110 mg starting dose level of PF-05212384. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF 05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Arm type	Experimental
Investigational medicinal product name	PF-05212384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. After one cycle of dosing with PF-05212384, in subsequent cycles, the dose level remained at 110 mg or was escalated based on the occurrences of dose limiting toxicities (DLTs) in previous cycle and at the discretion of the investigator. Subjects enrolled in Korea remained at the 110 mg starting dose level of PF-05212384.

Investigational medicinal product name	Irinotecan hydrochloride trihydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2.

Arm title	Cetuximab + Irinotecan: Arm B

Arm description:

Cetuximab was administered IV every week (Days 1, 8, 15 and 22 of each 28-day cycle) at a starting dose level of 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 in subsequent infusions. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level

of 180 mg/m^2. Both the dose levels of cetuximab and irinotecan were adjusted according to severity of toxicities.

Arm type	Active comparator
Investigational medicinal product name	Irinotecan hydrochloride trihydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab was administered IV every week (Days 1, 8, 15 and 22 of each 28-day cycle) at a starting dose level of 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 in subsequent infusions.

Arm title	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)

Arm description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF-05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Arm type	Experimental
Investigational medicinal product name	Irinotecan hydrochloride trihydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2.

Investigational medicinal product name	PF-05212384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23.

Number of subjects in period 1	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)
Started	7	6	6
Completed	0	0	0
Not completed	7	6	6
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	2	-
Protocol amendment	1	3	6
Study terminated by sponsor	4	-	-
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PF-05212384 + Irinotecan: Arm A

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF 05212384 was only dosed on Days 9, 16 and 23. After one cycle of dosing with PF-05212384, in subsequent cycles, the dose level remained at 110 mg or was escalated based on the occurrences of dose limiting toxicities (DLTs) in previous cycle and at the discretion of the investigator. Subjects enrolled in Korea remained at the 110 mg starting dose level of PF-05212384. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF 05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Reporting group title	Cetuximab + Irinotecan: Arm B

Reporting group description:

Cetuximab was administered IV every week (Days 1, 8, 15 and 22 of each 28-day cycle) at a starting dose level of 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 in subsequent infusions. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of cetuximab and irinotecan were adjusted according to severity of toxicities.

Reporting group title	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF-05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Reporting group values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)
Number of subjects	7	6	6
Age Categorical Units: Subjects			
<18 years	0	0	0
18-64 years	5	4	4
>=65 years	2	2	2
Age continuous Units: years			
arithmetic mean	59.4	61.5	60.3
standard deviation	± 7.8	± 6.1	± 6.7
Gender, Male/Female Units: Subjects			
FEMALE	4	3	4
MALE	3	3	2

Reporting group values	Total		
Number of subjects	19		
Age Categorical Units: Subjects			
<18 years	0		
18-64 years	13		

>=65 years	6		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender, Male/Female Units: Subjects			
FEMALE	11		
MALE	8		

End points

End points reporting groups

Reporting group title	PF-05212384 + Irinotecan: Arm A

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF 05212384 was only dosed on Days 9, 16 and 23. After one cycle of dosing with PF-05212384, in subsequent cycles, the dose level remained at 110 mg or was escalated based on the occurrences of dose limiting toxicities (DLTs) in previous cycle and at the discretion of the investigator. Subjects enrolled in Korea remained at the 110 mg starting dose level of PF-05212384. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF 05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Reporting group title	Cetuximab + Irinotecan: Arm B

Reporting group description:

Cetuximab was administered IV every week (Days 1, 8, 15 and 22 of each 28-day cycle) at a starting dose level of 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 in subsequent infusions. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of cetuximab and irinotecan were adjusted according to severity of toxicities.

Reporting group title	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF-05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Primary: Progression Free Survival (PFS) as Assessed by Investigators

End point title	Progression Free Survival (PFS) as Assessed by

End point description:

Progression-free survival (PFS) was the time from the first dose of study treatment to the first documentation of objective tumor progression or death due to any cause, whichever occurred first. Objective progression was defined as 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum was observed during therapy), with a minimum absolute increase of 5 mm. Median PFS was estimated based on the Kaplan-Meier method. Per protocol analysis set was used for analysis of this end point, and it included all subjects who were randomized, with KRAS and NRAS wild type status confirmed by our central lab, and with treatment arm assignment designated according to randomization.

End point type	Primary

End point timeframe:

36 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: Due to early termination of this study and therefore limited data, no statistical analysis was conducted on this primary end point.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3[3]		
Units: months				
median (confidence interval 95%)	3.7 (1.5 to 7.4)	16.6 (0.9999 to 99999)		

Notes:

[3] - Only one non-censored data point, the CI range is set from 0.9999 to 99999 as it was not computed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Objective Response

End point title	Number of Subjects With Objective Response

End point description:

Number of subjects with objective response was based on assessment of confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1. Confirmed PR was defined as disappearance of all target lesions. Confirmed PR was defined as >=30% decrease in sum of the longest dimensions of the target lesions taking the baseline sum as a reference. Confirmed responses were those that persisted on repeat imaging study >=4 weeks after initial documentation of response. Response evaluable analysis set was used for analysis of this end point, and it included all subjects in the full analysis set (all subjects who were randomized, with treatment arm assignments designated according to randomization) who had an adequate baseline assessment of disease and measurable disease.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects	1	3	0	

Statistical analyses

Statistical analysis title	Objective response in Arm A versus Arm B
Comparison groups	Cetuximab + Irinotecan: Arm B v PF-05212384 + Irinotecan: Arm A

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.164
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	-35.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.4
upper limit	12

Secondary: Number of Subjects With Unacceptable Toxicity in Cycle 1 (Japanese LIC only)

End point title	Number of Subjects With Unacceptable Toxicity in Cycle 1 (Japanese LIC only)[4]

End point description:

Unacceptable toxicity (according to Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0) was any of the following occurrences: (1) grade 4 neutropenia >7 days, or febrile neutropenia, or grade 4 thrombocytopenia; (2) grade >=3 nausea/vomiting despite optimal antiemetic treatment, or grade >=3 diarrhea despite optimal anti diarrheal treatment; (3) unmanageable grade >=3 hyperglycemia; (4) mean QTc interval (time from electrocardiogram [ECG] Q wave to the end of the T wave corresponding to electrical systole, corrected for heart rate) >501 msec in triplicate 12-lead ECG, or myocardial infarction, or ventricular arrhythmia; (5) grade >=3 non-hematologic toxicity; (6) treatment delay of >=2 weeks due to study drug related toxicity; (7) persistent, intolerable toxicities which resulted in failure to deliver at least 75% of doses of both PF-05212384 and irinotecan during Cycle 1; (8) grade >=2 respiratory toxicities. All subjects enrolled into Japanese LIC were included.

End point type	Secondary

End point timeframe:

28 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As indicated in this end point title, data were collected only in the Japanese Lead-In Cohort.

End point values	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response[5]

End point description:

For subjects with an objective response (CR or PR), duration of response was defined as the time from first documentation of CR or PR to date of first documentation of objective progression or death. Date of first documentation of progression and date of first documentation of CR or PR were based on Investigator assessment of response. All subjects who achieved CR or PR in Arm A and Arm B were included for analysis of this end point

End point type	Secondary

End point timeframe:

2 years

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[6]	3[7]		
Units: months				
median (confidence interval 95%)	5.6 (0.9999 to 99999)	14.8 (0.9999 to 99999)		

Notes:

[6] - Only one non-censored data point, the CI range is set from 0.9999 to 99999 as it was not computed.
[7] - Only one non-censored data point, the CI range is set from 0.9999 to 99999 as it was not computed.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[8]

End point description:

Overall survival (OS) was defined as the duration from enrollment to death. Subjects last known to be alive were censored at date of last contact. Per protocol analysis set was used for analysis of this end point, and it included all subjects who were randomized, with KRAS and NRAS wild type status confirmed by central lab and with treatment arm assignment designated according to randomization.

End point type	Secondary

End point timeframe:

2 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[9]	3[10]		
Units: months				
median (confidence interval 95%)	99999 (3.3 to 99999)	99999 (99999 to 99999)		

Notes:

[9] - Only 1 subject had evaluable value, and 99999 was used as the high range value.

[10] - No subject had evaluable value, and 99999 was entered instead.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An SAE was defined as any untoward occurrence at any dose that resulted in death; was life threatening (immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); resulted in congenital anomaly/birth defect. AEs included both serious and non-serious AEs. Treatment-emergent AEs were those with initial onset or increasing in severity after the first dose of study drug. Safety analysis set was used for analysis of this end point, and it included all subjects who received at least one dose of study drug, with treatment arm assignment designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Administration of the first dose of study drug through 28 calendar days after the last administration of study drug

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
AEs	7	6	6	
SAEs	3	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Common Terminology Criteria for Adverse Events (CTCAE) Grade

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Common Terminology Criteria for Adverse Events (CTCAE) Grade

End point description:

TEAEs were those AEs with initial onset or increasing in severity after the first dose of study drug.

CTCAE version 4.0 was used to grade the severity of TEAEs. Grade 1 referred to mild AEs; grade 2 referred to moderate AEs; grade 3 referred to severe AEs; grade 4 referred to AEs with life-threatening consequences, and urgent intervention was needed to manage them; grade 5 referred to death related to AE. Safety analysis set was used for the analysis of this end point, and it included all subjects who received at least one dose of study treatment, with treatment arm assignment designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Administration of the first dose of study drug through 28 calendar days after the last administration of study drug

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
Grade 1	1	2	2	
Grade 2	1	1	0	
Grade 3	3	2	4	
Grade 4	2	0	0	
Grade 5	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test (Hematology) Abnormalities

End point title	Number of Subjects With Laboratory Test (Hematology) Abnormalities

End point description:

The following hematology parameters were evaluated in this study: hemoglobin, white blood cells (WBC) with differential, and platelets. Safety analysis set was used for the analysis of this end point, and it included all subjects who received at least one dose of study treatment, with treatment arm assignment designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
Anemia	6	6	6	

Hemoglobin increased	0	0	0	
Lymphocyte count increased	0	2	0	
Lymphopenia	5	4	5	
Neutrophils (absolute)	4	3	5	
Platelets	0	3	1	
White blood cells	4	4	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Laboratory Test (Chemistry) Abnormalities

End point title	Number of Subjects with Laboratory Test (Chemistry) Abnormalities

End point description:

The following chemistry parameters were evaluated in this study: sodium, potassium, magnesium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, albumin, blood urea nitrogen (BUN) or urea, creatinine, total calcium, glycosylated hemoglobin (HbA1c), glucose, uric acid, phosphorus or phosphate, insulin, and C-peptide. Safety analysis set was used for the analysis of this end point, and it included all subjects who received at least one dose of study treatment, with treatment arm assignment designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
ALT	2	1	1	
Alkaline phosphatase	3	4	4	
AST	2	1	1	
Total bilirubin	0	1	0	
Creatitine	4	3	6	
Hypercalcemia	1	0	0	
Hyperglycemia	6	4	4	
Hyperkalemia	1	0	0	
Hypermagnesemia	0	0	0	
Hypernatremia	1	0	1	
Hypoalbuminemia	2	4	4	
Hypocalcemia	2	3	3	
Hypoglycemia	0	1	0	
Hypokalemia	2	2	3	
Hypomagnesemia	3	4	1	
Hyponatremia	2	1	0	

Hypophosphatemia	2	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test (Urinalysis) Abnormalities

End point title	Number of Subjects With Laboratory Test (Urinalysis) Abnormalities

End point description:

Urinalysis included urine dipstick for protein and blood: if positive, perform a microscopic analysis. Safety analysis set was used for the analysis of this end point, and it included all subjects who received at least one dose of study treatment, with treatment arm assignment designated according to actual study treatment received. Number of subjects with urine protein tested positive is presented.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects	3	1	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test (Coagulation) Abnormalities

End point title	Number of Subjects With Laboratory Test (Coagulation) Abnormalities

End point description:

Coagulation analysis included partial thromboplastin time (PTT) and international normalized ratio (INR) or prothrombin time (PT). Safety analysis set was used for the analysis of this end point, and it included all subjects who received at least one dose of study treatment, with treatment arm assignment designated according to actual study treatment received. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
PTT (n=7, 6, 5)	2	4	0	
PT (n=7, 5, 6)	3	3	1	
PT INR (n=7, 6, 6)	1	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With ECG Post-Baseline Maximum Absolute Values Meeting Pre-defined Criteria

End point title	Number of Subjects With ECG Post-Baseline Maximum Absolute Values Meeting Pre-defined Criteria

End point description:

The number of subjects with ECG post-baseline maximum absolute values meeting the following criteria was reported: (1) maximum QTc interval ranged from 450 to 480 msec; >480-500 msec; >500 msec; (2) maximum QTcB (QT corrected for heart rate using Bazett's formula) interval ranged from 450 to 480 msec; >480-500 msec; >500 msec; (3) maximum QTcF (QT corrected for heart rate using Fridericia's formula) interval ranged from 450 to 480 msec; >480-500 msec; >500 msec. QTc analysis set was used for analysis of this end point, and it included all subjects in the safety analysis set who had at least one ECG assessment after receiving study treatment.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	6	
Units: subjects				
Maximum QTc interval: 450-480 msec	2	1	1	
Maximum QTc interval: >480-500 msec	0	0	0	
Maximum QTc interval: >500 msec	0	0	0	
Maximum QTcB interval: 450-480 msec	3	1	0	
Maximum QTcB interval: >480-500 msec	0	0	0	
Maximum QTcB interval: >500 msec	0	0	0	
Maximum QTcF interval: >450-480 msec	1	0	0	

Maximum QTcF interval: >480-500 msec	0	0	0	
Maximum QTcF interval: >500 msec	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With ECG Maximum Increase From Baseline Meeting Pre-defined Criteria

End point title	Number of Subjects With ECG Maximum Increase From Baseline Meeting Pre-defined Criteria

End point description:

The number of subjects with ECG maximum increase from baseline meeting the following criteria was reported: Criterion A: maximum QTc interval increase from baseline >30 msec and ≤60 msec; criterion B: maximum QTc interval increase from baseline >60 msec; criterion C: maximum QTcB interval increase from baseline >30 msec and ≤60 msec; criterion D: maximum QTcB interval increase from baseline >60 msec; criterion E: maximum QTcF interval increase from baseline >30 msec and ≤60 msec; criterion F: maximum QTcF interval increase from baseline >60 msec. QTc analysis set was used for analysis of this end point, and it included all subjects in the safety analysis set who had at least one ECG assessment after receiving study treatment.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	3	6	
Units: subjects				
Criterion A	1	1	0	
Criterion B	0	0	0	
Criterion C	0	1	0	
Criterion D	0	0	0	
Criterion E	0	0	0	
Criterion F	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of PF-05212384

End point title	Maximum Plasma Concentration (Cmax) of PF-05212384[11]

End point description:

Cmax of PF-05212384 was observed directly from data. The pharmacokinetic (PK) concentration

analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects in Japanese LIC) who started treatment and had at least one time point with a concentration measurement recorded. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1, 2, 4, 6, 24, 72, 120 hours post PF-05212384 infusion on Cycle 1 Day 9 and Cycle 1 Day 16.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", because PF-05212384 was not administered to subjects in this arm as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 9 (n=6, 6)	8345 (± 19)	8534 (± 10)		
Cycle 1 Day 16 (n=5, 6)	10120 (± 27)	9670 (± 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Irinotecan

End point title	Maximum Plasma Concentration (Cmax) of Irinotecan[12]

End point description:

Cmax of irinotecan was observed directly from data. The PK concentration analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects in Japanese LIC) who started treatment and had at least one time point with a concentration measurement recorded. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle Day 1 (n=7, 6)	2283 (± 30)	2123 (± 18)		
Cycle 2 Day 1 (n=4, 5)	1620 (± 41)	1999 (± 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of SN-38

End point title	Maximum Plasma Concentration (Cmax) of SN-38[13]

End point description:

SN-38 is an irinotecan metabolite. Cmax of SN-38 was observed directly from data. The PK concentration analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects in Japanese LIC) who started treatment and had at least one time point with a concentration measurement recorded. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=7, 6)	23.51 (± 32)	24.25 (± 50)		
Cycle 2 Day 1 (n=4, 5)	22.81 (± 67)	28.04 (± 33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time for maximum plasma concentration (Tmax) of PF-05212384

End point title	Time for maximum plasma concentration (Tmax) of PF-05212384[14]

End point description:

Tmax of PF-05212384 was observed directly from data as time of first occurrence. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1, 2, 4, 6, 24, 72, 120 hours post PF-05212384 infusion on Cycle 1 Day 9 and Cycle 1 Day 16.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", because PF-05212384 was not administered to subjects in this arm as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 9 (n=6, 6)	0.483 (0.467 to 0.517)	0.483 (0.467 to 0.5)		
Cycle 1 Day 16 (n=5, 6)	0.5 (0.467 to 0.517)	0.5 (0.483 to 0.517)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time for maximum plasma concentration (Tmax) of Irinotecan

End point title	Time for maximum plasma concentration (Tmax) of

End point description:

Tmax of irinotecan was observed directly from data as time of first occurrence. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1 (n=7, 6)	1.5 (1.47 to 1.62)	1.53 (1.48 to 1.58)		
Cycle 2 Day 1 (n=4, 5)	1.55 (1.5 to 2.05)	1.53 (1.5 to 1.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time for maximum plasma concentration (Tmax) of SN-38

End point title	Time for maximum plasma concentration (Tmax) of SN-38[16]

End point description:

SN-38 is an irinotecan metabolite. Tmax of SN-38 was observed directly from data as time of first occurrence. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1 (n=7, 6)	2 (1.5 to 2.18)	1.98 (1.48 to 2.08)		
Cycle 2 Day 1 (n=4, 5)	2.03 (1.53 to 3.98)	1.93 (1.9 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t½) of PF-05212384

End point title	Terminal Elimination Half Life (t½) of PF-05212384[17]

End point description:

T½ was calculated as loge(2)/kel, where kel was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1, 2, 4, 6, 24, 72, 120 hours post PF-05212384 infusion on Cycle 1 Day 9 and Cycle 1 Day 16.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", because PF-05212384 was not administered to subjects in this arm as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours				
arithmetic mean (standard deviation)				
Cycle 1 Day 9 (n=6, 6)	37.65 (± 4.55)	37.78 (± 3.61)		
Cycle 1 Day 16 (n=4, 6)	35.1 (± 6.9)	36.07 (± 4.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t½) of Irinotecan

End point title	Terminal Elimination Half Life (t½) of Irinotecan[18]

End point description:

T½ was calculated as loge(2)/kel, where kel was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese

LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hours				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=7, 6)	5.547 (± 0.562)	5.255 (± 0.42)		
Cycle 2 Day 1 (n=4, 5)	5.293 (± 0.488)	5.344 (± 0.719)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t½) of SN-38

End point title	Terminal Elimination Half Life (t½) of SN-38[19]

End point description:

T½ was calculated as loge(2)/kel, where kel was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[20]	3		
Units: hours				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=2, 3)	99999 (± 99999)	9.89 (± 0.811)		
Cycle 2 Day 1 (n=2, 4)	99999 (± 99999)	8.84 (± 1.091)		

Notes:

[20] - No evaluable value, and 99999 was entered instead.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of PF-05212384

End point title	Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of PF-05212384[21]

End point description:

AUClast refers to the area under plasma concentration time profile from time zero to the time for the last quantifiable concentration. AUClast of PF-05212384 was determined using linear/log trapezoidal method. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1, 2, 4, 6, 24, 72, 120 hours post PF-05212384 infusion on Cycle 1 Day 9.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", because PF-05212384 was not administered to subjects in this arm as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	11530 (± 15)	13390 (± 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of Irinotecan

End point title	Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of Irinotecan[22]

End point description:

AUClast refers to the area under plasma concentration time profile from time zero to the time for the last quantifiable concentration. AUClast of irinotecan was determined using linear/log trapezoidal method. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=7, 6)	11860 (± 23)	11030 (± 29)		
Cycle 2 Day 1 (n=4, 5)	8776 (± 62)	10380 (± 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of SN-38

End point title	Area Under Plasma Concentration Time Profile From Time Zero to the Time for the Last Quantifiable Concentration (AUClast) of SN-38[23]

End point description:

AUClast refers to the area under plasma concentration time profile from time zero to the time for the last quantifiable concentration. AUClast of SN-38 (an irinotecan metabolite) was determined using linear/log trapezoidal method. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=7, 6)	217 (± 29)	217.9 (± 38)		
Cycle 2 Day 1 (n=4, 5)	182.4 (± 43)	228.5 (± 38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of PF-05212384

End point title	Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of PF-05212384[24]

End point description:

AUCinf refers to the area under plasma concentration time profile from time zero extrapolated to infinite time. AUCinf of PF-05212384 was calculated using the formula: AUCinf = AUClast + (Clast*/kel), where Clast* was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5, 1, 2, 4, 6, 24, 72, 120 hours post PF-05212384 infusion on Cycle 1 Day 9.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", because PF-05212384 was not administered to subjects in this arm as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	11700 (± 15)	13580 (± 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of Irinotecan

End point title	Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of Irinotecan[25]

End point description:

AUCinf refers to the area under plasma concentration time profile from time zero extrapolated to infinite time. AUCinf of irinotecan was calculated using the formula: AUCinf = AUClast + (Clast*/kel), where Clast* was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=7, 6)	12480 (± 23)	11570 (± 30)		
Cycle 2 Day 1 (n=4, 5)	9216 (± 63)	10950 (± 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of SN-38

End point title	Area Under Plasma Concentration Time Profile From Time Zero Extrapolated to Infinite Time (AUCinf) of SN-38[26]

End point description:

AUCinf refers to the area under plasma concentration time profile from time zero extrapolated to infinite time. AUCinf of SN-38 (an irinotecan metabolite) was calculated using the formula: AUCinf = AUClast + (Clast*/kel), where Clast* was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. The PK parameter analysis set was used for analysis of this end point, and it included all randomized subjects (or enrolled subjects to the Japanese LIC) who started treatment and had at least one of the PK parameters of interest estimated. Here, n in parentheses represents the number of subjects who were evaluable for each category in each arm. As pre-specified in protocol, this end point was not analyzed for reporting arm: "Cetuximab + Irinotecan: Arm B".

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1.5, 2, 4, 6 and 24 hours post irinotecan infusion on Cycle 1 Day 1 and Cycle 2 Day 1.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "Cetuximab + Irinotecan: Arm B", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[27]	3		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=2, 3)	99999 (± 99999)	230.4 (± 13)		
Cycle 2 Day 1 (n=2, 4)	99999 (± 99999)	279.7 (± 45)		

Notes:

[27] - No evaluable value, and 99999 was entered instead.

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of signaling proteins in paired and single tumor biopsies

End point title	Levels of signaling proteins in paired and single tumor biopsies

End point description:

Pre defined signaling proteins included Akt (protein kinase B), p-Akt (phosphorylated Akt), p-S6 (phosphorylated ribosomal protein S6), p-Met (phosphorylated Met, a receptor tyrosine kinase), p-mTOR (phosphorylated mammalian target of rapamycin), EGFR (epithelial growth factor receptor), and p-EGFR (phosphorylated EGFR).

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: ng/g				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[28] - This endpoint was not analyzed due to early termination of this study.

[29] - This endpoint was not analyzed due to early termination of this study.

[30] - This endpoint was not analyzed due to early termination of this study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Expression of Pre-defined Gene Sequences in Biopsied Tumor Tissues

End point title	Number of Subjects With Expression of Pre-defined Gene Sequences in Biopsied Tumor Tissues

End point description:

Pre-defined gene sequences were those related to EGFR, PI3K (phosphoinositide-3 kinase) and other oncogenic pathways; examples included but were not limited to PIK3CA (this gene encodes the catalytic subunit of PI3K), PIK3R1 (this gene encodes the regulatory subunit of PI3K), KRAS, NRAS and BRAF (this gene encodes serine/threonine-protein kinase B-Raf) sequences and PIK3CA gene amplification. Due to early termination of this study, these pre-defined gene sequences were not analyzed, except for KRAS and NRAS. Number of subjects who had KRAS and NRAS wild type status confirmed by the central laboratory is presented. All subjects for whom at least one of these pre-defined gene sequences was analyzed were included. Here, number of subjects analyzed represents the total number of subjects enrolled into each arm, and n refers to the number of subjects who had measurements for each category.

End point type	Secondary

End point timeframe:

2 years

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: subjects				
Confirmed wild type KRAS (n=4, 3, 6)	4	3	6	
Confirmed wild type NRAS (n=4, 3, 3)	4	3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-

Colorectal (FACT-C)

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Colorectal (FACT-C)[31]

End point description:

Functional Assessment of Cancer Therapy-Colorectal (FACT-C) was used in this study to assess Health-Related Quality of Life (HRQoL) and CRC-related symptoms in subjects enrolled to the randomized portion of the study. The FACT-C is part of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system, a comprehensive and extensive set of self-reported instruments for the assessment of health-related quality of life in subjects with cancer or other chronic illnesses. All subjects enrolled into the randomized portion of this study (ie, reporting arm A and B) were included. however, this outcome measure was not summarized due to early termination of this study. Here, number of subjects analyzed represents the total number of subjects enrolled into each arm.

End point type	Secondary

End point timeframe:

2 years

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was not analyzed for reporting arm "PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)", as pre-specified in the protocol.

End point values	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[32]	6[33]		
Units: score on a scale	99999	99999		

Notes:

[32] - No evaluable value, and 99999 was entered instead.

[33] - No evaluable value, and 99999 was entered instead.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Administration of the first dose of study drug through 28 calendar days after the last administration of study drug

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	PF-05212384 + Irinotecan: Arm A

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. After one cycle of dosing with PF-05212384, in subsequent cycles, the dose level remained at 110 mg or was escalated based on the occurrences of dose limiting toxicities (DLTs) in previous cycle and at the discretion of the investigator. Subjects enrolled in Korea remained at the 110 mg starting dose level of PF-05212384. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF-05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Reporting group title	Cetuximab + Irinotecan: Arm B

Reporting group description:

Cetuximab was administered IV every week (Days 1, 8, 15 and 22 of each 28-day cycle) at a starting dose level of 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 in subsequent infusions. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of cetuximab and irinotecan were adjusted according to severity of toxicities.

Reporting group title	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)

Reporting group description:

PF-05212384 was administered intravenously (IV) every week (Days 2, 9, 16 and 23 of each 28-day cycle) at a starting dose level of 110 mg. During Cycle 1, PF-05212384 was only dosed on Days 9, 16 and 23. Irinotecan was administered IV every other week (Days 1 and 15 of each 28-day cycle) at a dose level of 180 mg/m^2. Both the dose levels of PF-05212384 and irinotecan were adjusted according to severity of toxicities. Infusion of PF-05212384 followed irinotecan infusion by at least 24 hours (+/- 10%).

Serious adverse events	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	1 / 6 (16.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PF-05212384 + Irinotecan: Arm A	Cetuximab + Irinotecan: Arm B	PF-05212384 + Irinotecan: Japanese Lead-In Cohort (LIC)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	7	0	0
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	10	2	1
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	5
Mucosal inflammation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	6	1	1
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dry throat			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Hiccups			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pulmonary embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Laceration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	8	5	0
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	2	4	6
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			

subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Abdominal pain lower			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Colitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Colonic fistula			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	4	4	0
Diarrhoea			
subjects affected / exposed	5 / 7 (71.43%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	17	16	3
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Anal incontinence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	6 / 7 (85.71%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	14	4	5
Stomatitis			
subjects affected / exposed	5 / 7 (71.43%)	1 / 6 (16.67%)	4 / 6 (66.67%)
occurrences (all)	9	1	4
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	6	1	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Nail disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Pruritus			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Rash			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	2	1	2
Rash pruritic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Infections and infestations			
Anorectal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	6	2	5
Dehydration			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Diabetes mellitus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			

subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Hyperuricaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2013	Objective to observe anti-tumor activity in the Japanese lead in cohort subjects was added; clarification was added to sections regarding acceptable KRAS test methods, in order to more closely match cetuximab drug labeling.
28 January 2014	Additional language was added to section 5.2.2 to specify timing between reconstitution of PF-05212384 and infusion.
29 May 2014	Intra-subject PF-05212384 dose escalation was added for subjects who are tolerating treatment at the lower dose levels; revision was made to timing of second biopsy for those subjects enrolled to Arm A.
10 December 2014	Rationale for enrollment termination was added, and information regarding handling of ongoing subjects was added; changes to procedures after enrollment termination were added; language was added regarding data handling and analysis after termination of enrollment.

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.

This study was terminated by sponsor due to strategic reasons and not due to any safety or efficacy concerns with treatment of PF-05212384.

Notes: