Clinical trial results:
A Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib Versus Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Subjects With Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus.

Summary

EudraCT number	2010-021336-33
Trial protocol	DE ES FI IE AT IT GB BE NL DK PT NO
Global end of trial date	30 November 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	A8081014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01154140
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., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, 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	16 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that crizotinib (Arm A) is superior to first-line chemotherapy, pemetrexed/cisplatin or pemetrexed/carboplatin (Arm B), in prolonging progression free survival in subjects with advanced non-small cell lung cancer (NSCLC) whose tumors harbor a translocation or inversion event involving the ALK gene locus.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	72 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 39
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Japan: 32
Country: Number of subjects enrolled	Korea, Republic of: 55
Country: Number of subjects enrolled	Luxembourg: 2
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 1

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	343
EEA total number of subjects	107

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)	288
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with histologically or cytologically proven diagnosis of locally advanced, recurrent, or metastatic non squamous NSCLC and tumors with measurable disease were enrolled. Subjects were to be positive for translocation or inversion events involving the ALK gene locus as determined by an ALK break apart Fluorescence In-Situ Hybridization test.

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	Crizotinib

Arm description:

Crizotinib 250 milligram (mg) capsule, orally twice daily was administered in treatment cycle of 21 days. Subjects could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 defined progressive disease (PD), as determined by independent radiology review (IRR), at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Crizotinib 250 mg capsule administered orally twice daily in cycles of 21 days.

Arm title	Chemotherapy

Arm description:

Standard doses of chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) were administered intravenously on Day 1 of each cycle for a maximum of 6 cycles. Pemetrexed 500 mg per meter square (m)^2 intravenous (IV) infusion according to standard of care was administered over 10 minutes (min); either cisplatin 75 mg/m^2 IV infusion was administered approximately 30 min after the end of the pemetrexed infusion or carboplatin was administered at a dose calculated to produce an area under the concentration time curve (AUC) of 5 or 6 milligram*minute per millilitre (mg*min/mL), approximately 30 min after end of pemetrexed infusion.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 500 mg/m^2 IV infusion administered over 10 min according to standard of care.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin IV infusion administered at a dose calculated to produce an AUC of 5 or 6 mg*min/mL over 30 min according to standard of care.

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

Dosage and administration details:

Cisplatin 75 mg/m^2 IV infusion administered over 30 min according to standard of care.

Number of subjects in period 1	Crizotinib	Chemotherapy
Started	172	171
Treated	171	169
Completed	81	69
Not completed	91	102
Adverse event, serious fatal	71	81
Consent withdrawn by subject	12	13
Unspecified	3	1
Randomized,not treated	1	2
Lost to follow-up	4	5

Baseline characteristics

Reporting groups	
Reporting group title	Crizotinib

Reporting group description:

Crizotinib 250 milligram (mg) capsule, orally twice daily was administered in treatment cycle of 21 days. Subjects could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 defined progressive disease (PD), as determined by independent radiology review (IRR), at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit.

Reporting group title	Chemotherapy

Reporting group description:

Standard doses of chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) were administered intravenously on Day 1 of each cycle for a maximum of 6 cycles. Pemetrexed 500 mg per meter square (m)^2 intravenous (IV) infusion according to standard of care was administered over 10 minutes (min); either cisplatin 75 mg/m^2 IV infusion was administered approximately 30 min after the end of the pemetrexed infusion or carboplatin was administered at a dose calculated to produce an area under the concentration time curve (AUC) of 5 or 6 milligram*minute per millilitre (mg*min/mL), approximately 30 min after end of pemetrexed infusion.

Reporting group values	Crizotinib	Chemotherapy	Total
Number of subjects	172	171	343
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	149	139	288
From 65-84 years	23	32	55
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.9	52.9	
standard deviation	± 11.9	± 13.1	-
Gender, Male/Female Units: Subjects			
Female	104	108	212
Male	68	63	131

End points

End points reporting groups

Reporting group title	Crizotinib

Reporting group description:

Crizotinib 250 milligram (mg) capsule, orally twice daily was administered in treatment cycle of 21 days. Subjects could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 defined progressive disease (PD), as determined by independent radiology review (IRR), at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit.

Reporting group title	Chemotherapy

Reporting group description:

Standard doses of chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) were administered intravenously on Day 1 of each cycle for a maximum of 6 cycles. Pemetrexed 500 mg per meter square (m)^2 intravenous (IV) infusion according to standard of care was administered over 10 minutes (min); either cisplatin 75 mg/m^2 IV infusion was administered approximately 30 min after the end of the pemetrexed infusion or carboplatin was administered at a dose calculated to produce an area under the concentration time curve (AUC) of 5 or 6 milligram*minute per millilitre (mg*min/mL), approximately 30 min after end of pemetrexed infusion.

Primary: Progression-Free Survival (PFS) Based on IRR

End point title	Progression-Free Survival (PFS) Based on IRR

End point description:

PFS was defined as the time from the date of randomization in study until the date of first documented objective tumor progression (according to RECIST v1.1 as determined by IRR) or death (due to any cause), whichever occurred first. PFS was calculated as (first event date − randomization date +1)/30.44. Objective progression was defined as a 20 percent (%) increase in the sum of the diameters of target measurable lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), with a minimum absolute increase of 5 millimeter (mm) or clear progression of pre-existing non-target lesions or the appearance of any new clear lesions. Full Analysis (FA)= subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Primary

End point timeframe:

Randomization to objective progression, death or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (confidence interval 95%)	10.9 (8.3 to 13.9)	7 (6.8 to 8.2)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy
Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.454
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.596

Notes:

[1] - P-value was obtained from 1-sided log rank test, stratified by eastern cooperative oncology group performance status (ECOG PS),race,brain metastases. 1-sided log-rank test at 0.0247 level of significance was used to compare PFS between the 2 arms.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS (in months) was defined as the duration from start of study treatment to date of death due to any cause. OS =(date of death minus the date of randomization of study medication plus 1) divided by 30.4. For subjects who were alive, overall survival was censored on last date the subjects were known to be alive. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

From randomization to death or last date known alive for those not known to have died (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (confidence interval 95%)	99999 (45.8 to 99999)	47.5 (32.2 to 99999)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy
Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0489 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	1.053

Notes:

[2] - P-value was obtained from 1-sided log rank test, stratified by ECOG PS, race group and brain metastases.

Secondary: Overall Survival Probability at Month 12 and 18

End point title	Overall Survival Probability at Month 12 and 18

End point description:

Overall survival probability at Month 12 and 18 was defined as the probability of overall survival at 12 and 18 months respectively, where the OS was defined as the duration from start of study treatment to date of death due to any cause. The survival probability was estimated using the Kaplan-Meier method. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Month 12, 18

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: percent probability				
number (confidence interval 95%)				
Month 12	83.5 (77 to 88.3)	78.4 (71.3 to 83.9)		
Month 18	71.5 (64 to 77.7)	66.6 (58.8 to 73.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR): Percentage of Subjects With Objective Response as Assessed by IRR

End point title	Objective Response Rate (ORR): Percentage of Subjects With Objective Response as Assessed by IRR

End point description:

ORR was defined as percentage of subjects with complete response (CR) or partial response (PR) according to RECIST v1.1 determined by IRR. CR was defined as complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must decrease to normal (short axis less than [<] 10 mm). No new lesions and disappearance of all non-target lesions. PR was defined as greater than or equal to (>=) 30% decrease taking as reference the baseline sum of lesion dimensions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. No clear progression of non-target disease. No new lesions. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Randomization to objective progression, death or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: percentage of subjects				
number (confidence interval 95%)	74.4 (67.2 to 80.8)	45 (37.4 to 52.8)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

If the PFS endpoint was significant, ORR was to be considered significant if the 2-sided p-value from Pearson chi-square test was (less than or equal to)<= 0.0494.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [3]
Method	Pearson chi-square test
Parameter estimate	Difference in percentage
Point estimate	29.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.5
upper limit	39.3

Notes:

[3] - P-value was obtained from a Pearson chi-square test

Secondary: Duration of Response (DR) Based on IRR

End point title	Duration of Response (DR) Based on IRR

End point description:

Time from first documentation of objective tumor response(CR or PR)to first documentation of PD or death due to any cause,whichever occurred first as per RECISTv1.1 determined by IRR.CR:complete disappearance of all target and non-target disease.All nodes(target, non-target)must decrease to normal(short axis <10 mm).No new lesions,disappearance of all non-target lesions.PR:>=30% decrease taking as reference the baseline sum of lesion dimensions.Short axis was used in sum for target nodes,while longest diameter was used in sum for all or target lesions.No clear progression of non-target disease.c)PD:20 % increase in the sum of the diameters of target measurable lesions taking as reference the smallest sum on study(includes the baseline sum if that is the smallest on study)with a minimum absolute increase of 5 mm or clear progression of pre-existing non-target lesions or the appearance of any new clear lesions.FA set.N=subjects with objective tumor response evaluable for the

End point type	Secondary

End point timeframe:

From objective response to date of progression, death or last tumor assessment without progression

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	77		
Units: weeks				
median (confidence interval 95%)	49 (35.1 to 60)	22.9 (18 to 25.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) Based on IRR

End point title	Time to tumor response (TTR) Based on IRR

End point description:

TTR was defined as the time from randomization to first documentation of objective tumor response (CR or PR) according to RECIST v1.1 determined by IRR. CR: complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must decrease to normal (short axis <10 mm). No new lesions and disappearance of all non-target lesions. PR: >=30% decrease taking as reference the baseline sum of lesion dimensions. Short axis was used in sum for target nodes, while longest diameter was used in sum for all or target lesions. No clear progression of non-target disease. No new lesions. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization. Here "N" signifies subjects with objective tumor response and were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Randomization to first documentation of objective tumor response (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	77		
Units: weeks				
median (full range (min-max))	6.1 (2.7 to 41.4)	12.1 (5.1 to 36.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Control at Week 12 Based on IRR

End point title	Percentage of Subjects With Disease Control at Week 12 Based on IRR

End point description:

Disease control rate at week 12 is defined as the percent of subjects with CR, PR, or stable disease (SD) at week 12 according to RECIST v1.1 determined by IRR. The best response of SD would be assigned if SD criteria was met at least once after randomization at a minimum interval of 6 weeks. CR: complete disappearance of all target lesions and non-target disease, with exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis <10 mm). No new lesions and disappearance of all non-target lesions. PR: >=30% decrease taking as reference the baseline sum of lesion dimensions. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters. Short axis was used in sum for target nodes, while longest diameter was used in sum for all or target lesions. No clear progression of non-target disease. No new lesions. FA analysis set.

End point type	Secondary

End point timeframe:

Week 12

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: percentage of subjects				
number (confidence interval 95%)	78.5 (71.6 to 84.4)	68.4 (60.9 to 75.3)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

The confidence interval for the difference in percentage was based on normal distribution

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0381
Method	Pearson chi-square test
Parameter estimate	Difference in percentage
Point estimate	10.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	19.4

Secondary: Time to progression (TTP) Based on IRR

End point title	Time to progression (TTP) Based on IRR

End point description:

TTP was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression according to RECIST v1.1 determined by IRR. Objective tumor progression was defined as 20% increase in the sum of the diameters of target measurable lesions taking as

reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), with a minimum absolute increase of 5 mm or clear progression of pre-existing non-target lesions, or the appearance of any new clear lesions. If tumor progression data included more than 1 date, the first date was used. TTP (in months) was calculated as (first event date − randomization date +1)/30.44. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Randomization to objective progression or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (confidence interval 95%)	13.6 (8.5 to 15)	7 (6.8 to 8.3)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

Analysis was based on the Cox Proportional hazards model assuming proportional hazards, a HR less than 1 indicated a reduction in hazard rate in favor of Crizotinib.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.441
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.335
upper limit	0.582

Notes:

[4] - P-value was obtained from 1-sided unstratified log-rank test.

Secondary: Time to Intracranial Progression (IC-TTP) Based on IRR

End point title	Time to Intracranial Progression (IC-TTP) Based on IRR

End point description:

IC-TTP was defined similarly to TTP, but only considering intracranial disease (excluding extracranial disease) and the progression was determined based on either new brain metastases or progression of existing brain metastases. TTP was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression according to RECIST v1.1 determined by IRR. Objective tumor progression was defined as 20% increase in the sum of the diameters of target measurable lesions taking as reference the smallest sum on study (this includes the baseline sum if that

is the smallest on study), with a minimum absolute increase of 5 mm or clear progression of pre-existing non-target lesions, or the appearance of any new clear lesions. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Randomization to objective intracranial progression or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	17.8 (13.9 to 99999)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

Analysis was based on the Cox Proportional hazards model assuming proportional hazards, a HR less than 1 indicated a reduction in hazard rate in favor of Crizotinib.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0347 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.595
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.338
upper limit	1.048

Notes:

[5] - P-value was obtained from 1-sided unstratified log-rank test.

Secondary: Time to Extracranial Progression (EC-TTP) Based on IRR

End point title	Time to Extracranial Progression (EC-TTP) Based on IRR

End point description:

EC-TTP was defined similarly to TTP, but only considering extracranial disease (excluding intracranial disease) and the progression was determined based on either new extracranial lesions or progression of existing extracranial lesions. TTP was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression according to RECIST v1.1 determined by IRR. Objective tumor progression was defined as 20% increase in the sum of the diameters of target measurable lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), with a minimum absolute increase of 5 mm or clear progression of pre-existing non-target lesions, or the appearance of any new clear lesions. FA population included all

subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Randomization to objective extracranial progression or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: months				
median (confidence interval 95%)	15.2 (12.6 to 21.9)	7.2 (6.9 to 8.5)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

Analysis was based on the Cox Proportional hazards model assuming proportional hazards, a HR less than 1 indicated a reduction in hazard rate in favor of Crizotinib.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.387
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.286
upper limit	0.524

Notes:

[6] - P-value was obtained from 1-sided unstratified log-rank test.

Secondary: Percentage of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose of study drug that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. The safety analysis population included all randomized subjects who received at least 1 dose of study treatment, with treatment assignments designated according to actual

study treatment received during the first cycle.

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	169		
Units: percentage of subjects				
number (not applicable)				
AEs	99.4	99.4		
SAEs	41.5	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 28 days after last dose of study drug that were absent before treatment or that worsened relative to pre-treatment state. Relatedness to study drug was assessed by the investigator. The safety analysis population included all randomized subjects who received at least 1 dose of study treatment, with treatment assignments designated according to actual study treatment received during the first cycle.

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	169		
Units: percentage of subjects				
number (not applicable)				
AEs	98.2	92.3		
SAEs	12.9	8.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) According to Maximum Severity

End point title	Percentage of Subjects With Adverse Events (AEs) According to Maximum Severity

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. AE was assessed according to maximum severity grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0. Grade 1 =mild; Grade 2 =moderate; within normal limits, Grade 3 =severe or medically significant but not immediately life-threatening; Grade 4 =life-threatening or disabling; urgent intervention indicated; Grade 5 =death. The safety analysis population included all randomized subjects who received at least 1 dose of study treatment, with treatment assignments designated according to actual study treatment received during the first cycle.

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	169		
Units: percentage of subjects				
number (not applicable)				
Grade 1	7	9.5		
Grade 2	28.7	34.3		
Grade 3	41.5	44.4		
Grade 4	8.8	8.9		
Grade 5	13.5	2.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Predose Concentration (Ctrough) of Crizotinib and its Metabolite PF-06260182

End point title	Plasma Predose Concentration (Ctrough) of Crizotinib and its Metabolite PF-06260182[7]

End point description:

Ctrough is the concentration prior to study drug administration on Day 1 of Cycle 2 onwards. PF-06260182 is the metabolite of Crizotinib. The Pharmacokinetic concentration population included all

subjects in the safety analysis population who had at least 1 plasma concentration of crizotinib or its metabolite.N= subjects who were evaluable for this measure. n= subjects who were evaluable at specified time points. This analysis was performed in crizotinib arm only.

End point type	Secondary

End point timeframe:

Predose at Day 1 of Cycle 2, 3 and 5

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to be reported for Crizotinib arm only.

End point values	Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Crizotinib Ctrough: Cycle 2 Day 1 (n= 91)	324.2 (± 39)			
Crizotinib Ctrough: Cycle 3 Day 1 (n= 85)	320.9 (± 40)			
Crizotinib Ctrough: Cycle 5 Day 1 (n= 82)	308.2 (± 39)			
PF-06260182 Ctrough: Cycle 2 Day 1 (n= 100)	98.4 (± 46)			
PF-06260182 Ctrough: Cycle 3 Day 1 (n= 94)	99 (± 49)			
PF-06260182 Ctrough: Cycle 5 Day 1 (n= 86)	92.9 (± 55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects For Each Anaplastic Lymphoma Kinase (ALK) Gene Fusion Variants

End point title	Percentage of Subjects For Each Anaplastic Lymphoma Kinase (ALK) Gene Fusion Variants

End point description:

The Response Genetics, Inc. Echinoderm Microtubule Associated Protein Like 4 (EML4) ALK reverse transcriptase polymerase chain reaction (RT PCR) gene fusion test was used for the analysis of tissue samples for the ALK gene fusion variants (either no rearrangement, or 1 of 9 results reflecting 8 specific rearrangements [V1, V2, V3a, V3b,V3a/b, V4, V5a, V6, V7]). Percentage of subjects who tested positive for ALK gene fusion variants were reported in this endpoint. The ALK variant evaluable population included subjects from the FA population who had a result from ALK gene fusion variant testing of either no rearrangement, or 1 of 9 results reflecting 8 specific rearrangements (V1, V2, V3a, V3b, V3a/b, V4, V5a, V6, and V7).

End point type	Secondary

End point timeframe:

28 days prior to day 1 of study treatment

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	78		
Units: percentage of subjects				
number (not applicable)				
V1	27.1	25.6		
V2	7.1	7.7		
V3a	1.4	1.3		
V3a/b	4.3	6.4		
No rearrangement	60	59		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) of Anaplastic Lymphoma Kinase (ALK) Variant Groups Based on IRR

End point title	Objective Response Rate (ORR) of Anaplastic Lymphoma Kinase (ALK) Variant Groups Based on IRR

End point description:

The Response Genetics, Inc. EML4 ALK RTPCR gene fusion test was used for the analysis of tissue samples for the ALK gene fusion variants (either no rearrangement, or 1 of 9 results reflecting 8 specific rearrangements [V1, V2, V3a, V3b,V3a/b, V4, V5a, V6, V7]). Percentage of subjects with confirmed CR or PR according to RECIST v1.1 determined by IRR, by type of ALK gene fusion variant were reported in this outcome measure. CR: complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must decrease to normal (short axis<10 mm).No new lesions and disappearance of all non-target lesions.PR:>=30% decrease taking as reference the baseline sum of lesion dimensions. Short axis was used in sum for target nodes, while longest diameter was used in sum for all or target lesions. No clear progression of non-target disease. No new lesions. The ALK variant evaluable set. Here, n signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Randomization to objective progression, death or last tumor assessment without progression before any additional anti-cancer therapy (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	78		
Units: percentage of subjects				
number (confidence interval 95%)				
V1 (n =19,20)	84.2 (60.4 to 96.6)	45 (23.1 to 68.5)		
V2 (n =5,6)	100 (47.8 to 100)	33.3 (4.3 to 77.7)		
V3a (n =1,1)	0 (-99999 to 99999)	100 (2.5 to 100)		
V3a/b (n =3,5)	100 (29.2 to 100)	60 (14.7 to 94.7)		
No rearrangement (n =42,46)	71.4 (55.4 to 84.3)	43.5 (28.9 to 58.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Chest Pain, Dyspnea or Cough

End point title	Time to Deterioration (TTD) in Chest Pain, Dyspnea or Cough

End point description:

TTD in pain in chest, dyspnea, or cough from the Quality of Life Questionnaire Core 30 (QLQ-LC13) was a composite endpoint defined as the time from randomization to the earliest time the subject scale scores showed a 10 point or greater increase after baseline in any of the 3 symptoms. For those who had not shown deterioration, the data was censored at the last date when the subjects completed an assessment (QLQ-LC13) for pain, dyspnea, or cough or at last visit date prior to crossover for subjects randomized to chemotherapy who crossed over to crizotinib. A 10-point or higher change in the score was perceived by subjects as clinically significant. The transformed score of pain, dyspnea, and cough symptom scales of EORTC (European Organization for the Research and Treatment of Cancer) QLQ-LC13 range from 0 to 100, where higher scores indicate greater symptom severity. The patient reported outcome (PRO) evaluable analysis set.

End point type	Secondary

End point timeframe:

From randomization of treatment up to deterioration while on study treatment (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	163		
Units: months				
median (confidence interval 95%)	2.1 (0.8 to 4.2)	0.5 (0.4 to 0.7)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

HR was calculated based on the Cox Proportional hazards model. Assuming proportional hazards, a HR less than 1 indicated a reduction in hazard rate in favor of crizotinib.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0002 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.591

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.452
upper limit	0.773

Notes:

[8] - Two-sided p-value from the unstratified log rank test was used.

Secondary: Change From Baseline in Functioning and Global Quality of Life (QOL) as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point title	Change From Baseline in Functioning and Global Quality of Life (QOL) as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point description:

EORTC QLQ-C30: included 5 functional scales (physical, role, cognitive, emotional and social), global health status/global quality of life scale, 3 symptom scales (fatigue, pain, nausea and vomiting), 6 single items that assess the additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea) and financial difficulties. All scales and single-item measures range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, for the global health status/QoL represents a high QoL (better subject state), and for a symptom scale/item represents a high level of symptoms/problems (worse subject state). PRO evaluable population included all subjects from the FA population who completed a baseline and at least 1 postbaseline PRO assessment prior to end of randomized study treatment.

End point type	Secondary

End point timeframe:

Baseline, From Cycle 1 Day 1 up to end of study treatment or crossover to crizotinib arm (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	163		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
QLQ-C30 Global QoL	5.9815 (3.92 to 8.05)	-7.8488 (-10.15 to -5.55)		
QLQ-C30 Cognitive Functioning	1.1836 (-0.66 to 3.03)	-2.1696 (-4.21 to -0.13)		
QLQ-C30 Emotional Functioning	8.7431 (6.77 to 10.72)	1.2266 (-0.95 to 3.4)		
QLQ-C30 Physical Functioning	5.937 (3.94 to 7.93)	-4.4664 (-6.59 to -2.34)		
QLQ-C30 Role Functioning	4.8122 (1.92 to 7.71)	-10.7391 (-13.87 to -7.61)		
QLQ-C30 Social Functioning	4.379 (1.6 to 7.15)	-4.3851 (-7.37 to -1.4)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 Global QoL: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	13.8303
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.74
upper limit	16.92

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 cognitive functioning: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.017
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.3532
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	6.11

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 emotional functioning: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	7.5165
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.57
upper limit	10.46

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 physical functioning: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	10.4035
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.48
upper limit	13.32

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 role functioning: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	15.5513

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.29
upper limit	19.81

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 social functioning: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.7641
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.69
upper limit	12.84

Secondary: Change From Baseline Scores in QLQ-C30 Symptoms as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point title	Change From Baseline Scores in QLQ-C30 Symptoms as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point description:

EORTC QLQ-C30: included 5 functional scales (physical, role, cognitive, emotional and social), global health status/global quality of life scale, 3 symptom scales (fatigue, pain, nausea and vomiting), 6 single items that assess the additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea) and financial difficulties. All scales and single-item measures range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, for the global health status/QoL represents a high QoL (better subject state), and for a symptom scale/item represents a high level of symptoms/problems (worse subject state). The PRO evaluable population included all subjects from the FA population who completed a baseline and at least 1 postbaseline PRO assessment prior to crossover to crizotinib or end of randomized study treatment.

End point type	Secondary

End point timeframe:

Baseline, From Cycle 1 Day 1 up to end of study treatment or crossover to crizotinib arm (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	163		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
QLQ-C30 Appetite loss	-5.4906 (-8.52 to -2.47)	8.007 (4.63 to 11.38)		
QLQ-C30 Constipation	6.4858 (3.46 to 9.51)	10.9194 (7.5 to 14.34)		
QLQ-C30 Diarrhea	12.9558 (10.67 to 15.24)	0.4652 (-2.2 to 3.13)		
QLQ-C30 Dysponea	-14.9019 (-17.4 to -12.4)	-1.4398 (-4.21 to 1.33)		
QLQ-C30 Fatigue	-7.3476 (-9.72 to -4.98)	7.6511 (5.05 to 10.25)		
QLQ-C30 Financial Difficulties	-0.5984 (-3.13 to 1.93)	0.2203 (-2.54 to 2.98)		
QLQ-C30 Insomnia	-10.3095 (-13.1 to -7.52)	-0.2665 (-3.38 to 2.84)		
QLQ-C30 Nausea and Vomiting	3.7742 (1.54 to 6.01)	7.2188 (4.66 to 9.78)		
QLQ-C30 Pain	-11.0993 (-13.27 to -8.92)	-1.1716 (-3.66 to 1.31)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 appetite loss: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-13.4976
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.03
upper limit	-8.97

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 constipation: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.057
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.4336
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	0.13

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 diarrhea: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	12.4906
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.98
upper limit	16

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 dysponea: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-13.4622
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	-9.73

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 fatigue: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-14.9987
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.52
upper limit	-11.48

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 financial difficulties: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6681
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.8186

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	2.92

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 insomnia: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-10.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.22
upper limit	-5.87

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-C30 nausea and vomiting: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0468
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.4446
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.84
upper limit	-0.05

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:	
QLQ-C30 pain: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).	
Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-9.9277
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.23
upper limit	-6.62

Secondary: Change From Baseline in Lung Cancer Symptom Scores as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (QLQ- LC13)

End point title	Change From Baseline in Lung Cancer Symptom Scores as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (QLQ- LC13)

End point description:

QLQ-LC13 consists of 1 multi-item scale and 9 single items that assess the specific symptoms (dyspnea, cough, hemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of patients with lung cancer receiving chemotherapy. All multi-item scales and single-item measures range from 0 to 100, where higher score indicates greater degree of symptom severity. The PRO evaluable population included all subjects from the FA population who completed a baseline and at least 1 postbaseline PRO assessment prior to crossover to crizotinib or end of randomized study treatment.

End point type	Secondary

End point timeframe:

Baseline, From Cycle 1 day 1 up to end of study treatment or crossover to crizotinib arm (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	163		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
QLQ-LC13 Alopecia	-4.4879 (-6.99 to -1.99)	0.3271 (-2.4 to 3.06)		
QLQ-LC13 Coughing	-16.4819 (-18.92 to -14.05)	-8.0893 (-10.83 to -5.35)		
QLQ-LC13 Dysphagia	0.7618 (-0.82 to 2.35)	0.0966 (-1.76 to 1.95)		

QLQ-LC13 Dyspnoea	-9.2029 (-11.2 to -7.2)	-0.1948 (-2.36 to 1.97)		
QLQ-LC13 Haemoptysis	-3.2197 (-3.83 to -2.61)	-2.3369 (-3.05 to -1.62)		
QLQ-LC13 Pain in Arm or Shoulder	-10.1693 (-12.26 to -8.08)	-4.1218 (-6.51 to -1.74)		
QLQ-LC13 Pain in Chest	-8.1437 (-10.31 to -5.98)	-0.0479 (-2.48 to 2.38)		
QLQ-LC13 Pain in Other Parts	-8.0757 (-10.28 to -5.87)	-1.304 (-3.97 to 1.36)		
QLQ-LC13 Peripheral Neuropathy	3.1779 (1.04 to 5.31)	-0.1742 (-2.6 to 2.25)		
QLQ-LC13 Sore Mouth	2.2472 (0.36 to 4.13)	4.3993 (2.27 to 6.53)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 alopecia: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0108
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.8149
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.52
upper limit	-1.11

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 coughing: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.3926
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.06
upper limit	-4.72

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 dysphagia: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5938
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.6651
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	3.11

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 dyspnoea: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-9.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.96
upper limit	-6.06

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 haemoptysis: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0656
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.8828
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	0.06

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 pain in arm or shoulder: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-6.0475
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.22
upper limit	-2.88

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 pain in chest: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.0959
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.35
upper limit	-4.84

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 pain in other parts: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-6.7717
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.24
upper limit	-3.31

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 peripheral neuropathy: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0427
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.3521
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	6.59

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

QLQ-LC13 sore mouth: Analysis was from a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC13 subscale baseline score (intercept and time from first dose are included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1382
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.1521
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	0.69

Secondary: Change From Baseline in General Health Status as Assessed by EuroQol 5D (EQ-5D)- Visual Analog Scale (VAS)

End point title	Change From Baseline in General Health Status as Assessed by EuroQol 5D (EQ-5D)- Visual Analog Scale (VAS)

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single index value. VAS component: subjects rated their current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health. The PRO evaluable population included all subjects from the FA population who completed a baseline and at least 1 postbaseline PRO assessment prior to crossover to crizotinib or end of randomized study treatment. Here, "N" signifies participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, From Cycle 1 day 1 up to end of study treatment or crossover to crizotinib arm (up to 35 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	160		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	4.5323 (2.44 to 6.62)	0.5415 (-1.85 to 2.93)		

Statistical analyses

Statistical analysis title	Crizotinib vs Chemotherapy

Statistical analysis description:

Analysis was based on a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EQ-5D VAS subscale baseline score (intercept and time from first dose were included as random effects).

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0139
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.9908
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	7.17

Secondary: Percentage of Subjects with Hospital Admissions-Healthcare Resource Utilization (HCRU)

End point title	Percentage of Subjects with Hospital Admissions-Healthcare Resource Utilization (HCRU)

End point description:

Healthcare resource utilization was to be evaluated using the assessment of the following: date and duration of index admission, duration of hospitalization and date of discharge. FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization.

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	171		
Units: percentage of subjects				
number (not applicable)	40.12	36.26		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 1 to 4 Hematological Test Abnormalities

End point title	Percentage of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 1 to 4 Hematological Test Abnormalities

End point description:

Anemia (grade[g]1:Less than[<]Lower limit of normal[LLN] to 10gram per[/]deciliter[g/dL],g2:<10 to 8g/dL,g3:<8g/dL,g4:lifethreatening); platelet (g1:<LLN to 75*10^3/mm]^3,g2:<75*10^3/mm^3 to 50*10^3/mm^3,g3:<50*10^3/mm^3 to 25*10^3/mm^3,g4:<25*10^3/mm^3);lymphopenia(g1:<LLN to 8*10^2/mm^3,g2:<8*10^2 to 5*10^2/mm^3,g3:<5*10^2 to 2*10^2/mm^3,g4:<2*10^2/mm^3); neutrophil(g1:<LLN to 15*10^2/mm^3,g2:<15*10^2 to 10*10^2/mm^3,g3:<10*10^2 to 5*10^2/mm^3,g4:<5*10^2/mm^3);WBC(g1:<LLN to 3*10^3/mm^3,g2:<3*10^3 to 2*10^3/mm^3,g3:<2*10^3 to 1*10^3/mm^3,g4:<1*10^3/mm^3); haemoglobin (Hgb) (g1:increase in Hgb level>0 to 2 g/dL above ULN or above baseline if baseline is above ULN,g2:increase in Hgb level>2 to 4g/dL above ULN or above baseline if baseline is above ULN,g3:increase in Hgb level>4 g/dL above ULN or above baseline if baseline is above ULN). Subject>=1 abnormality given. Safety analysis

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	165		
Units: percentage of subjects				
number (not applicable)				
Anemia: Grade 1	47.1	46.7		
Anemia: Grade 2	13.5	27.9		
Anemia: Grade 3	0.6	10.9		
Hemoglobin increased: Grade 1	6.5	3		
Hemoglobin increased: Grade 2	0.6	0		
Lymphocyte count increased: Grade 2	3.5	1.2		
Lymphopenia: Grade 1	34.1	26.1		
Lymphopenia: Grade 2	24.7	33.9		
Lymphopenia: Grade 3	10.6	13.9		
Lymphopenia: Grade 4	2.4	1.8		
Neutrophils (Absolute): Grade 1	20.6	14.5		
Neutrophils (Absolute): Grade 2	20	26.7		

Neutrophils (Absolute): Grade 3	14.1	13.9		
Neutrophils (Absolute): Grade 4	0.6	3.6		
Platelets: Grade 1	9.4	21.8		
Platelets: Grade 2	2.4	7.9		
Platelets: Grade 3	0.6	7.9		
Platelets: Grade 4	0	0.6		
White blood cells: Grade 1	23.5	34.5		
White blood cells: Grade 2	22.5	24.2		
White blood cells: Grade 3	2.9	9.1		
White blood cells: Grade 4	0	0.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 1 to 4 Chemistry Test Abnormalities

End point title	Percentage of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 1 to 4 Chemistry Test Abnormalities

End point description:

ALT/AST([g]1:>ULN-3*ULN,g2:>3-5*ULN,g3:>5-20*ULN,g4:>20*ULN);AP(g1:>ULN-2.5*ULN,g2:>2.5-5*ULN,g3:>5-20*ULN,g4:>20*ULN);CR(g1:>ULN-1.5*ULN,g2:>1.5-3*ULN,g3:>3-6*ULN,g4:>6*ULN);hyperglycemia(g1:>ULN-160,g2:>160-250,g3:>250-500,g4:>500mg/dL);bilirubin(total) (g1:>ULN-1.5*ULN,g2:>1.5-3*ULN,g3:>3-10*ULN,g4:>10*ULN);hypoglycaemia (g1:<LLN-55,g2:<55-40,g3:<40-30,g4:<30mg/dL);hyperkalemia (g1:>ULN-5.5,g2:>5.5-6,g3:>6-7,g4:>7mmol/L);hypokalemia (g1:<LLN-3,g2:<LLN-3,g3:<3-2.5,g4:<2.5mmol/L);hypermagnesemia (g1:>ULN-3,g3:>3-8,g4:>8mg/dL);hypocalcemia (g1:<LLN-8,g2:<8-7,g3:<7-6,g4:<6mg/dL);hypercalcemia (g1:>ULN-11.5,g2:>11.5-12.5,g3:>12.5-13.5,g4:>13.5mg/dL);hypomagnesemia (g1:<LLN-1.2,g2:<1.2-0.9,g3:<0.9-0.7,g4:<0.7mg/dL);hyponatremia (g1:<LLN-130,g3:<130-120,g4:<120mmol/L);hypoalbuminemia (g1:<LLN-3,g2:<3-2,g3:<2,g4:lifethreatening);hypophosphatemia (g1:<LLN-2.5,g2:<2.5-2,g3:<2-1,g4:<1mg/dL).Safety set.N= subjects evaluable for this endpoint,n=subjects evaluable at specific time

End point type	Secondary

End point timeframe:

Baseline up to follow up period (up to 72 months)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	165		
Units: percentage of subjects				
number (not applicable)				
Alanine aminotransferase: Grade 1 (n =171, 165)	64.3	34.5		
Alanine aminotransferase: Grade 2 (n =171, 165)	10.5	7.3		
Alanine aminotransferase: Grade 3 (n =171, 165)	12.3	1.8		

Alanine aminotransferase: Grade 4 (n =171, 165)	2.3	0		
Alkaline phosphatase: Grade 1 (n =171, 165)	55.6	33.9		
Alkaline phosphatase: Grade 2 (n =171, 165)	8.8	4.8		
Alkaline phosphatase: Grade 3 (n =171, 165)	0.6	1.2		
Aspartate Aminotransferase: Grade 1 (n =171, 165)	57.9	32.1		
Aspartate Aminotransferase: Grade 2 (n =171, 165)	6.4	1.8		
Aspartate Aminotransferase: Grade 3 (n =171, 165)	7.6	1.2		
Aspartate Aminotransferase: Grade 4 (n =171, 165)	0.6	0		
Bilirubin: Grade 1 (n =171, 165)	10.5	7.3		
Bilirubin: Grade 2 (n =171, 165)	5.8	1.2		
Bilirubin: Grade 3 (n =171, 165)	0	0.6		
Creatinine: Grade 1 (n =171, 165)	50.3	78.8		
Creatinine: Grade 2 (n =171, 165)	47.4	15.8		
Creatinine: Grade 3 (n =171, 165)	1.2	0		
Hypercalcemia: Grade 1 (n =171, 165)	0.6	9.1		
Hypercalcemia: Grade 4 (n =171, 165)	0.6	0		
Hyperglycemia: Grade 1 (n =171, 165)	50.3	42.4		
Hyperglycemia: Grade 2 (n =171, 165)	15.8	23.6		
Hyperglycemia: Grade 3 (n =171, 165)	4.1	3.6		
Hyperkalemia: Grade 1 (n =171, 165)	17.5	12.1		
Hyperkalemia: Grade 2 (n =171, 165)	5.8	3		
Hyperkalemia: Grade 3 (n =171, 165)	2.3	1.8		
Hyperkalemia: Grade 4 (n =171, 165)	0.6	0		
Hypermagnesemia: Grade 1 (n =170, 162)	17.6	8		
Hypermagnesemia: Grade 3 (n =170, 162)	1.8	0		
Hypernatremia: Grade 1 (n =171, 165)	21.1	5.5		
Hypernatremia: Grade 2 (n =171, 165)	0.6	0		
Hypernatremia: Grade 4 (n =171, 165)	0.6	0		
Hypoalbuminemia: Grade 1 (n =171, 164)	35.1	22.6		
Hypoalbuminemia: Grade 2 (n =171, 164)	44.4	14.6		
Hypoalbuminemia: Grade 3 (n =171, 164)	1.2	0.6		
Hypocalcemia: Grade 1 (n =171, 165)	39.8	24.8		
Hypocalcemia: Grade 2 (n =171, 165)	38	4.8		
Hypocalcemia: Grade 3 (n =171, 165)	2.3	0.6		
Hypoglycemia: Grade 1 (n =171, 165)	19.9	3.6		
Hypoglycemia: Grade 2 (n =171, 165)	4.7	1.8		
Hypoglycemia: Grade 4 (n =171, 165)	0	0.6		
Hypokalemia: Grade 1 (n =171, 165)	14.6	9.1		
Hypokalemia: Grade 3 (n =171, 165)	2.3	3		
Hypokalemia: Grade 4 (n =171, 165)	0	0.6		
Hypomagnesemia: Grade 1 (n =170, 162)	12.4	26.5		
Hypomagnesemia: Grade 2 (n =170, 162)	0	1.9		

Hyponatremia: Grade 1 (n =171, 165)	25.7	22.4		
Hyponatremia: Grade 3 (n =171, 165)	4.1	5.5		
Hyponatremia: Grade 4 (n =171, 165)	0.6	1.2		
Hypophosphatemia: Grade 1 (n =169, 161)	5.3	3.1		
Hypophosphatemia: Grade 2 (n =169, 161)	27.2	13		
Hypophosphatemia: Grade 3 (n =169, 161)	13	6.8		
Hypophosphatemia: Grade 4 (n =169, 161)	1.2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow up period (up to 72 months)

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 subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Chemotherapy

Reporting group description:

Standard doses of chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) were administered intravenously, where pemetrexed 500 mg/m^2 IV infusion according to standard of care was administered over 10 min; cisplatin 75mg/m^2 IV infusion was administered approximately 30 min after the end of the pemetrexed infusion and carboplatin was administered at a dose calculated to produce an AUC of 5 or 6 mg*min/mL, approximately 30 minutes after end of pemetrexed infusion.

Reporting group title	Crizotinib

Reporting group description:

Crizotinib 250 mg capsule, orally twice daily was administered in treatment cycle of 21 days (up to a maximum of 50 cycles). Subjects could continue crizotinib treatment beyond the time of RECIST v1.1 defined PD, as determined by IRR, at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit.

Serious adverse events	Chemotherapy	Crizotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 169 (28.99%)	71 / 171 (41.52%)	
number of deaths (all causes)	81	71	
number of deaths resulting from adverse events	4	23	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid adenoma			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 169 (0.59%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Orthostatic hypotension			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy	Additional description: This adverse event is gender specific.		
subjects affected / exposed[1]	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 169 (0.59%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			

subjects affected / exposed	1 / 169 (0.59%)	18 / 171 (10.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 19	
deaths causally related to treatment / all	1 / 1	18 / 18	
Fatigue			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 169 (1.18%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 169 (1.18%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed[2]	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Asthma			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 169 (2.37%)	7 / 171 (4.09%)	
occurrences causally related to treatment / all	0 / 4	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 169 (1.18%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 169 (0.59%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 169 (2.96%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 169 (4.14%)	5 / 171 (2.92%)	
occurrences causally related to treatment / all	2 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute respiratory distress syndrome			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypomania			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 169 (0.59%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 169 (1.18%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 169 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			

subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 169 (2.96%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 169 (1.18%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 169 (0.59%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 169 (0.59%)	4 / 171 (2.34%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 169 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 169 (2.37%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	5 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			

subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 169 (0.00%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscle spasms			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			

subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 169 (0.59%)	3 / 171 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 169 (0.59%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	2 / 2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 169 (0.59%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 169 (0.00%)	2 / 171 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 169 (1.18%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypokalaemia			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 169 (0.59%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	0 / 169 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: As this adverse event is gender specific, so the number of subjects at risk is equal to the number of female subjects in the study.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: As this adverse event is gender specific, so the number of subjects at risk is equal to the number of female subjects in the study.

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

Non-serious adverse events	Chemotherapy	Crizotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	165 / 169 (97.63%)	168 / 171 (98.25%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 169 (23.67%)	28 / 171 (16.37%)	
occurrences (all)	71	47	
Chest pain			
subjects affected / exposed	14 / 169 (8.28%)	21 / 171 (12.28%)	
occurrences (all)	18	26	
Fatigue			
subjects affected / exposed	66 / 169 (39.05%)	54 / 171 (31.58%)	
occurrences (all)	105	99	
Mucosal inflammation			
subjects affected / exposed	9 / 169 (5.33%)	2 / 171 (1.17%)	
occurrences (all)	11	2	
Oedema peripheral			
subjects affected / exposed	12 / 169 (7.10%)	89 / 171 (52.05%)	
occurrences (all)	18	189	
Pyrexia			

subjects affected / exposed	17 / 169 (10.06%)	40 / 171 (23.39%)	
occurrences (all)	24	61	
Influenza like illness			
subjects affected / exposed	1 / 169 (0.59%)	10 / 171 (5.85%)	
occurrences (all)	1	14	
Pain			
subjects affected / exposed	5 / 169 (2.96%)	9 / 171 (5.26%)	
occurrences (all)	9	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 169 (16.57%)	44 / 171 (25.73%)	
occurrences (all)	35	75	
Haemoptysis			
subjects affected / exposed	6 / 169 (3.55%)	11 / 171 (6.43%)	
occurrences (all)	7	13	
Dyspnoea			
subjects affected / exposed	23 / 169 (13.61%)	31 / 171 (18.13%)	
occurrences (all)	32	45	
Oropharyngeal pain			
subjects affected / exposed	8 / 169 (4.73%)	14 / 171 (8.19%)	
occurrences (all)	8	18	
Productive cough			
subjects affected / exposed	8 / 169 (4.73%)	15 / 171 (8.77%)	
occurrences (all)	9	18	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 169 (5.33%)	10 / 171 (5.85%)	
occurrences (all)	10	14	
Insomnia			
subjects affected / exposed	15 / 169 (8.88%)	23 / 171 (13.45%)	
occurrences (all)	21	26	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 169 (12.43%)	59 / 171 (34.50%)	
occurrences (all)	48	184	
Aspartate aminotransferase increased			

subjects affected / exposed	16 / 169 (9.47%)	47 / 171 (27.49%)	
occurrences (all)	30	120	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 169 (1.18%)	11 / 171 (6.43%)	
occurrences (all)	2	21	
Neutrophil count decreased			
subjects affected / exposed	17 / 169 (10.06%)	14 / 171 (8.19%)	
occurrences (all)	44	58	
Platelet count decreased			
subjects affected / exposed	19 / 169 (11.24%)	1 / 171 (0.58%)	
occurrences (all)	33	1	
Weight decreased			
subjects affected / exposed	5 / 169 (2.96%)	12 / 171 (7.02%)	
occurrences (all)	7	31	
Weight increased			
subjects affected / exposed	4 / 169 (2.37%)	16 / 171 (9.36%)	
occurrences (all)	9	34	
White blood cell count decreased			
subjects affected / exposed	12 / 169 (7.10%)	11 / 171 (6.43%)	
occurrences (all)	25	84	
Blood bilirubin increased			
subjects affected / exposed	2 / 169 (1.18%)	9 / 171 (5.26%)	
occurrences (all)	4	21	
Blood creatinine increased			
subjects affected / exposed	5 / 169 (2.96%)	9 / 171 (5.26%)	
occurrences (all)	5	9	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 169 (0.00%)	22 / 171 (12.87%)	
occurrences (all)	0	33	
Sinus bradycardia			
subjects affected / exposed	1 / 169 (0.59%)	10 / 171 (5.85%)	
occurrences (all)	1	11	
Nervous system disorders			
Dizziness			

subjects affected / exposed	15 / 169 (8.88%)	35 / 171 (20.47%)	
occurrences (all)	25	54	
Dysgeusia			
subjects affected / exposed	9 / 169 (5.33%)	45 / 171 (26.32%)	
occurrences (all)	9	64	
Headache			
subjects affected / exposed	25 / 169 (14.79%)	48 / 171 (28.07%)	
occurrences (all)	30	74	
Neuropathy peripheral			
subjects affected / exposed	12 / 169 (7.10%)	4 / 171 (2.34%)	
occurrences (all)	12	4	
Paraesthesia			
subjects affected / exposed	8 / 169 (4.73%)	29 / 171 (16.96%)	
occurrences (all)	11	36	
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 169 (5.92%)	6 / 171 (3.51%)	
occurrences (all)	14	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	53 / 169 (31.36%)	18 / 171 (10.53%)	
occurrences (all)	101	27	
Leukopenia			
subjects affected / exposed	16 / 169 (9.47%)	8 / 171 (4.68%)	
occurrences (all)	47	21	
Thrombocytopenia			
subjects affected / exposed	14 / 169 (8.28%)	1 / 171 (0.58%)	
occurrences (all)	36	1	
Neutropenia			
subjects affected / exposed	36 / 169 (21.30%)	32 / 171 (18.71%)	
occurrences (all)	107	203	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	10 / 169 (5.92%)	4 / 171 (2.34%)	
occurrences (all)	10	4	
Eye disorders			

Photopsia			
subjects affected / exposed	2 / 169 (1.18%)	18 / 171 (10.53%)	
occurrences (all)	2	30	
Vision blurred			
subjects affected / exposed	5 / 169 (2.96%)	13 / 171 (7.60%)	
occurrences (all)	5	16	
Visual impairment			
subjects affected / exposed	5 / 169 (2.96%)	98 / 171 (57.31%)	
occurrences (all)	5	123	
Vitreous floaters			
subjects affected / exposed	1 / 169 (0.59%)	11 / 171 (6.43%)	
occurrences (all)	1	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 169 (4.73%)	25 / 171 (14.62%)	
occurrences (all)	8	37	
Abdominal pain upper			
subjects affected / exposed	10 / 169 (5.92%)	27 / 171 (15.79%)	
occurrences (all)	17	34	
Constipation			
subjects affected / exposed	51 / 169 (30.18%)	78 / 171 (45.61%)	
occurrences (all)	68	135	
Diarrhoea			
subjects affected / exposed	22 / 169 (13.02%)	111 / 171 (64.91%)	
occurrences (all)	25	269	
Dyspepsia			
subjects affected / exposed	5 / 169 (2.96%)	27 / 171 (15.79%)	
occurrences (all)	7	41	
Dysphagia			
subjects affected / exposed	3 / 169 (1.78%)	19 / 171 (11.11%)	
occurrences (all)	4	25	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 169 (3.55%)	14 / 171 (8.19%)	
occurrences (all)	7	18	
Nausea			

subjects affected / exposed	98 / 169 (57.99%)	100 / 171 (58.48%)	
occurrences (all)	206	246	
Stomatitis			
subjects affected / exposed	17 / 169 (10.06%)	13 / 171 (7.60%)	
occurrences (all)	28	23	
Vomiting			
subjects affected / exposed	57 / 169 (33.73%)	87 / 171 (50.88%)	
occurrences (all)	89	223	
Abdominal distension			
subjects affected / exposed	1 / 169 (0.59%)	11 / 171 (6.43%)	
occurrences (all)	1	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	17 / 169 (10.06%)	16 / 171 (9.36%)	
occurrences (all)	18	17	
Rash			
subjects affected / exposed	20 / 169 (11.83%)	22 / 171 (12.87%)	
occurrences (all)	23	27	
Pruritus			
subjects affected / exposed	10 / 169 (5.92%)	9 / 171 (5.26%)	
occurrences (all)	11	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 169 (6.51%)	25 / 171 (14.62%)	
occurrences (all)	12	42	
Back pain			
subjects affected / exposed	20 / 169 (11.83%)	35 / 171 (20.47%)	
occurrences (all)	25	58	
Muscle spasms			
subjects affected / exposed	2 / 169 (1.18%)	17 / 171 (9.94%)	
occurrences (all)	2	21	
Bone pain			
subjects affected / exposed	4 / 169 (2.37%)	12 / 171 (7.02%)	
occurrences (all)	4	24	
Musculoskeletal pain			

subjects affected / exposed	8 / 169 (4.73%)	21 / 171 (12.28%)	
occurrences (all)	12	26	
Pain in extremity			
subjects affected / exposed	14 / 169 (8.28%)	44 / 171 (25.73%)	
occurrences (all)	17	61	
Flank pain			
subjects affected / exposed	2 / 169 (1.18%)	9 / 171 (5.26%)	
occurrences (all)	2	11	
Muscular weakness			
subjects affected / exposed	4 / 169 (2.37%)	9 / 171 (5.26%)	
occurrences (all)	4	14	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 169 (2.96%)	10 / 171 (5.85%)	
occurrences (all)	7	12	
Myalgia			
subjects affected / exposed	6 / 169 (3.55%)	14 / 171 (8.19%)	
occurrences (all)	8	16	
Neck pain			
subjects affected / exposed	2 / 169 (1.18%)	11 / 171 (6.43%)	
occurrences (all)	2	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 169 (2.96%)	30 / 171 (17.54%)	
occurrences (all)	6	63	
Upper respiratory tract infection			
subjects affected / exposed	13 / 169 (7.69%)	41 / 171 (23.98%)	
occurrences (all)	15	99	
Conjunctivitis			
subjects affected / exposed	10 / 169 (5.92%)	3 / 171 (1.75%)	
occurrences (all)	11	4	
Bronchitis			
subjects affected / exposed	2 / 169 (1.18%)	11 / 171 (6.43%)	
occurrences (all)	4	15	
Rhinitis			
subjects affected / exposed	2 / 169 (1.18%)	9 / 171 (5.26%)	
occurrences (all)	2	11	

Urinary tract infection			
subjects affected / exposed	2 / 169 (1.18%)	10 / 171 (5.85%)	
occurrences (all)	2	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	58 / 169 (34.32%)	59 / 171 (34.50%)	
occurrences (all)	108	99	
Hypoalbuminaemia			
subjects affected / exposed	2 / 169 (1.18%)	19 / 171 (11.11%)	
occurrences (all)	5	31	
Hypomagnesaemia			
subjects affected / exposed	13 / 169 (7.69%)	3 / 171 (1.75%)	
occurrences (all)	17	3	
Hypocalcaemia			
subjects affected / exposed	1 / 169 (0.59%)	10 / 171 (5.85%)	
occurrences (all)	1	14	
Hypophosphataemia			
subjects affected / exposed	2 / 169 (1.18%)	10 / 171 (5.85%)	
occurrences (all)	2	13	
Hypoproteinaemia			
subjects affected / exposed	0 / 169 (0.00%)	10 / 171 (5.85%)	
occurrences (all)	0	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2015	Extended survival followup period to 36 months after the randomization of the last subject, to enhance the likelihood to obtain an estimate of the median overall survival.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported