Clinical trial results:
Randomised, multicenter, Phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib.

Summary

EudraCT number	2015-000634-29
Trial protocol	PT ES DE SK HU FR PL BE BG IT
Global end of trial date	13 August 2018

Results information

Result version number	v2 (current)
This version publication date	22 August 2019
First version publication date	09 February 2018
Version creation reason	• New data added to full data set The study has completed and this update contains the full data set, including data collected after the first results upload to EudraCT.

Trial information

Trial identification

Sponsor protocol code	MO29750

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02604342
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: ALUR

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	13 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate and compare between treatment groups the efficacy of alectinib versus chemotherapy in subjects with ALK-positive advanced NSCLC who were previously treated with chemotherapy and crizotinib (progressed or intolerant to crizotinib), as measured by investigator-assessed Progression-free survival (PFS).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Turkey: 14
Worldwide total number of subjects	119
EEA total number of subjects	85

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)	92
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited subjects with Anaplastic Lymphoma Kinase(ALK)-positive advanced Non-Small Cell Lung Cancer(NSCLC) in 13 countries from November 2015 to January 2017.

Pre-assignment

Screening details:

A total of 142 subjects were screened, of which 119 were enrolled, 79 subjects in the alectinib arm and 40 in the chemotherapy arm.

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	Experimental: Alectinib

Arm description:

Subjects received oral alectinib at a dose of 600 milligrams (mg) twice daily, taken with food and treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or death.

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

Dosage and administration details:

Subjects received oral alectinib at a dose of 600 mg twice daily, taken with food until disease progression, unacceptable toxicity, withdrawal of consent or death.

Arm title	Active Comparator: Premetrexed/Docetaxel

Arm description:

Subjects received chemotherapy with either pemetrexed (500 milligrams per square meter [mg/m^2] of body surface area) or docetaxel (75 mg/m^2) intravenously.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received docetaxel at a dose of 75 mg/m^2 of body surface area intravenously every 3 weeks, until disease progression, unacceptable toxicity, withdrawal of consent or death.

Investigational medicinal product name	Premetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received pemetrexed at a dose of 500 mg/m^2 of body surface area intravenously every 3 weeks, until disease progression, unacceptable toxicity, withdrawal of consent or death.

Number of subjects in period 1	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel
Started	79	40
Completed	36	17
Not completed	43	23
Progression disease	1	-
Physician decision	2	-
Death	32	16
Not specified	1	-
Study termination by sponsor	1	-
Lost to follow-up	1	1
Withdrawal by subject	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Alectinib
Reporting group description:	
Subjects received oral alectinib at a dose of 600 milligrams (mg) twice daily, taken with food and treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or death.	
Reporting group title	Active Comparator: Premetrexed/Docetaxel
Reporting group description:	
Subjects received chemotherapy with either pemetrexed (500 milligrams per square meter [mg/m^2] of body surface area) or docetaxel (75 mg/m^2) intravenously.	

Reporting group values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel	Total
Number of subjects	79	40	119
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	54.6	58.8	
standard deviation	± 13.0	± 10.5	-
Sex: Female, Male Units: Subjects			
Female	33	20	53
Male	46	20	66
Ethnicity Units: Subjects			
Hispanic or Latino	5	4	9
Not Hispanic or Latino	68	34	102
Not reported	4	1	5
Unknown	0	1	1
Missing	2	0	2
Race Units: Subjects			
White	67	32	99
Asian	6	8	14
Unknown	5	0	5
Native Hawaiian or other Pacific Islander	1	0	1

End points

End points reporting groups

Reporting group title	Experimental: Alectinib
Reporting group description:	
Subjects received oral alectinib at a dose of 600 milligrams (mg) twice daily, taken with food and treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or death.	
Reporting group title	Active Comparator: Premetrexed/Docetaxel
Reporting group description:	
Subjects received chemotherapy with either pemetrexed (500 milligrams per square meter [mg/m^2] of body surface area) or docetaxel (75 mg/m^2) intravenously.	

Primary: Progression-Free Survival (PFS) Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator

End point title	Progression-Free Survival (PFS) Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator
End point description:	
PFS was defined as the time from randomisation to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurred first. As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 millimeter (mm) and the appearance of new lesions. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug.	
End point type	Primary
End point timeframe:	
Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)	

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: months				
median (confidence interval 95%)	10.9 (8.1 to 15.5)	1.4 (1.2 to 1.6)		

Statistical analyses

Statistical analysis title	Alectinib vs Premetrexed/Docetaxel
Statistical analysis description:	
Estimated hazard ratio obtained from stratified Cox model with treatment group as covariate.	
Comparison groups	Experimental: Alectinib v Active Comparator: Premetrexed/Docetaxel

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.33

Secondary: Percentage of Subjects With CNS Objective Response Rate (C-ORR) With Measurable CNS Metastases at Baseline Using RECIST Version 1.1 as Assessed By IRC

End point title	Percentage of Subjects With CNS Objective Response Rate (C-ORR) With Measurable CNS Metastases at Baseline Using RECIST Version 1.1 as Assessed By IRC

End point description:

Overall response rate in subjects with confirmed CNS response (C-ORR) was defined as the percentage of subjects who attained Complete Response (CR) or Partial Response (PR) for lesions in the CNS. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. Intent-to-treat population with measurable CNS metastasis (mC-ITT) included all subjects in ITT population with measurable CNS metastasis at baseline (as per IRC).

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	17		
Units: percentage of subjects				
number (not applicable)	66.7	0.0		

Statistical analyses

Statistical analysis title	C-ORR

Statistical analysis description:

95% confidence interval of the difference (alectinib - chemotherapy) computed using Hauck-Anderson approach.

Comparison groups	Experimental: Alectinib v Active Comparator:

	Premetrexed/Docetaxel
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Difference in C-ORR
Point estimate	0.667
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.86

Secondary: PFS Using RECIST Version 1.1 as Assessed by IRC

End point title	PFS Using RECIST Version 1.1 as Assessed by IRC

End point description:

PFS was defined as the time from randomisation to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurred first. As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 mm and the appearance of new lesions. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug.

This outcome measure was assessed as part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	35		
Units: months				
median (confidence interval 95%)	7.1 (6.3 to 10.8)	1.6 (1.3 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Objective Response of CR or PR Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point title	Percentage of Subjects with Objective Response of CR or PR Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point description:

ORR was defined as the percentage of subjects who attained CR or PR. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug.

The IRC assessment was part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: percentage of subjects				
number (not applicable)				
Assessed by Investigator	50.6	2.5		
Assessed by IRC (n=72, 35)	36.1	11.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disease Control Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point title	Percentage of Subjects with Disease Control Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point description:

Disease control rate (DCR) was defined as the percentage of subjects who attained CR, PR, or stable disease (SD) of at least 5 weeks. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters, SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters since the treatment started. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug.

The IRC assessment was part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: percentage of subjects				
number (not applicable)				
Assessed by Investigator	86.1	25.0		
Assessed by IRC	76.4	48.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point title	Duration of Response (DOR) Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point description:

DOR was defined as the time from when response (CR or PR) was first documented to first documented disease progression or death, whichever occurred first. DOR was evaluated for subjects who had a best overall response (BOR) of CR or PR. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. Here, "99999" indicates that the median and confidence interval was not reached due to less number of subjects with the event.

The IRC assessment was part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until PD, death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	1		
Units: months				
median (confidence interval 95%)				
Assessed by Investigator (n= 40, 1)	12.0 (8.3 to 23.5)	2.7 (-99999 to 99999)		
Assessed by IRC (n= 26, 4)	9.7 (5.6 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in C-ITT Population Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point title	PFS in C-ITT Population Using RECIST Version 1.1 as Assessed by Investigator and IRC

End point description:

PFS was defined as the time from randomisation to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurred first. As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 mm and the appearance of new lesions. Intent-to-treat population with CNS metastasis (C-ITT) included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). Here, "99999" indicates that the upper limit of confidence interval was not reached due to less number of subjects with the event.

This outcome measure assessment was part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: months				
median (confidence interval 95%)				
Assessed by Investigator	9.7 (6.9 to 99999)	1.4 (1.2 to 1.6)		
Assessed by IRC	8.1 (6.3 to 99999)	1.5 (1.2 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CNS progression in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point title	Time to CNS progression in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point description:

Time to CNS progression was defined as the time from randomisation until radiographic evidence of CNS progression.As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 mm and the appearance of new lesions. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). Here, "99999" indicates that the median and upper limit of confidence interval was not reached due to less number of subjects with the event.

This outcome measure assessment was part of the primary analysis and was not repeated during final analysis.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: months				
median (confidence interval 95%)	99999 (6.8 to 99999)	1.6 (1.3 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point title	Percentage of Participants With Disease Control in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point description:

DCR was defined as the percentage of subjects who attained CR, PR, or stable disease (SD) of at least 5 weeks. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters, SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters since the treatment started. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment).

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: percentage of subjects				
number (not applicable)	82.7	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With ORR in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point title	Percentage of Subjects With ORR in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC

End point description:

ORR was defined as the percentage of subjects who attained CR or PR. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. C-ITT included participants in ITT population with CNS metastasis at baseline (as per IRC assessment).

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: percentage of subjects				
number (not applicable)	48.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response for lesions in the CNS (C-DOR) Using RECIST Version 1.1 as Assessed by IRC

End point title	Duration of Response for lesions in the CNS (C-DOR) Using RECIST Version 1.1 as Assessed by IRC

End point description:

DOR was defined as the time from when response (CR or PR) was first documented to first documented disease progression or death, whichever occurred first. C-DOR was defined in a similar way for lesions in the CNS, taking into account all lesions in the body. DOR was evaluated for subjects who had a BOR of CR or PR. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). Here, "99999" indicates that the median and upper limit of confidence interval was not reached due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (Tumor assessments at baseline, every 6 weeks until progressive disease (PD), death or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[1]	28[2]		
Units: months				
median (confidence interval 95%)	13.9 (6.2 to 13.9)	99999 (99999 to 99999)		

Notes:

[1] - Number of subjects with CR or PR

[2] - Number of subjects with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomisation to death from any cause. OS was confounded by cross-over of subjects to the alectinib arm. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. Here, "99999" indicates that the median and confidence interval was not reached due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (Baseline until death)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: months				
median (confidence interval 95%)	27.8 (18.2 to 99999)	99999 (8.6 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Alectinib

End point title	Plasma Concentration of Alectinib[3]

End point description:

The Pharmacokinetic (PK) Evaluable Population included all subjects who received any dose of alectinib and who had at least one post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Predose (2 hours) at Baseline, Week 3 and Week 6

Notes:

[3] - 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: No formal hypothesis testing was planned for this study.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	559 (± 48.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) Over Time

End point title	Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) Over Time

End point description:

Percentage of subjects who filled out an EORTC QLQ-C30 questionnaire at a visit. The EORTC QLQ-C30 questionnaire consisted of 30 questions generating five functional scores (physical, role, cognitive, emotional, and social); a global health status/global quality of life scale score; three symptom scale scores (fatigue, pain, and nausea and vomiting); and six stand alone one-item scores that capture additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and perceived financial burden. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. 99999 indicates that data was not collected as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: percentage of subjects				
number (not applicable)				
Baseline	92.4	85.0		
Treatment - Week 3	96.1	83.3		
Treatment - Week 6	97.2	60.0		
Treatment - Week 12	95.5	80.0		
Treatment - Week 18	88.5	50.0		
Treatment - Week 24	91.1	100		
Treatment - Week 30	96.2	66.7		

Treatment - Week 36	89.8	66.7		
Treatment - Week 42	100	50		
Treatment - Week 48	100	100		
Treatment - Week 54	97.1	100		
Treatment - Week 60	100	100		
Treatment - Week 66	89.7	100		
Treatment - Week 72	88.9	100		
Treatment - Week 78	84.6	99999		
Treatment - Week 84	78.3	99999		
Treatment - Week 90	88.9	99999		
Treatment - Week 96	93.8	99999		
Treatment - Week 102	84.6	99999		
Treatment - Week 108	100	99999		
Treatment - Week 114	83.3	99999		
Treatment - Week 120	100	99999		
Treatment - Week 126	100	99999		
Treatment - Week 132	100	99999		
Treatment - Week 138	100	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Alectinib Metabolite

End point title	Plasma Concentration of Alectinib Metabolite[4]

End point description:

The PK Evaluable Population included all subjects who received any dose of alectinib and who had at least one post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Predose (2 hours) at Baseline, Week 3 and Week 6

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal hypothesis testing was planned for this study.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	240 (± 44.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-13 (EORTC QLQ-LC13) Over Time

End point title	Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-13 (EORTC QLQ-LC13) Over Time

End point description:

Percentage of subjects who filled out an EORTC QLQ-LC13 questionnaire at a visit. The EORTC QLQ-LC13 module generated one multiple-item scale score assessing dyspnea and a series of single item scores assessing chest pain, arm/shoulder pain, pain in other parts, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. 99999 indicates that data was not collected as no subject was evaluated at the specified time point.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: percentage of subjects				
number (not applicable)				
Baseline	92.4	82.5		
Treatment - Week 3	96.1	83.3		
Treatment - Week 6	97.2	63.3		
Treatment - Week 12	95.5	80.0		
Treatment - Week 18	88.5	50.0		
Treatment - Week 24	91.1	100		
Treatment - Week 30	96.2	66.7		
Treatment - Week 36	87.8	66.7		
Treatment - Week 42	95.3	66.7		
Treatment - Week 48	100	100		
Treatment - Week 54	97.1	100		
Treatment - Week 60	100	100		
Treatment - Week 66	89.7	100		
Treatment - Week 72	88.9	100		
Treatment - Week 78	84.6	99999		
Treatment - Week 84	78.3	99999		
Treatment - Week 90	88.9	99999		
Treatment - Week 96	100	99999		
Treatment - Week 102	84.6	99999		
Treatment - Week 108	100	99999		
Treatment - Week 114	83.3	99999		
Treatment - Week 120	80.0	99999		
Treatment - Week 126	100	99999		
Treatment - Week 132	100	99999		
Treatment - Week 138	100	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance of European Quality of Life (EuroQoL) 5 Dimension 5 Levels (EQ-5D-5L) Questionnaire Over Time

End point title	Compliance of European Quality of Life (EuroQoL) 5 Dimension 5 Levels (EQ-5D-5L) Questionnaire Over Time

End point description:

Percentage of subjects who filled out an EQ-5D-5L questionnaire at a visit. EQ-5D-5L: A generic preference-based health utility measure that provides a single index value for health status. The instrument consists of two parts. The first part, health-state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. "n" indicates number of subjects evaluated for specified time points. Here, "99999" indicates that the mean and standard deviation was not reached due to less number of subjects evaluated and no subject was evaluated for some time points.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	35		
Units: percentage of subjects				
number (not applicable)				
Treatment - Week 0 (n=72,35)	88.9	82.9		
Treatment - Week 3 (n=67,33)	86.6	78.8		
Treatment - Week 6 (n=62,29)	91.9	58.6		
Treatment - Week 12 (n=53,10)	86.8	80		
Treatment - Week 18 (n=43,6)	72.1	66.7		
Treatment - Week 24 (n=34,3)	82.4	100		
Treatment - Week 30 (n=25,3)	80	66.7		
Treatment - Week 36 (n=20,2)	80	50		
Treatment - Week 42 (n=12,2)	91.7	50		
Treatment - Week 48 (n=8,1)	62.5	0		
Treatment - Week 54 (n=3,0)	3	99999		
Treatment - Week 60 (n=2,0)	1	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for ITT Population

End point title	Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for ITT Population

End point description:

TTD in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for symptoms domains (or decrease for functioning domains from baseline for cough, dyspnea [single item and multi-item scales] chest pain [single item], pain in arm/shoulder and fatigue as measured by the EORTC QLQ-LC13. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. "n" indicates number of subjects evaluated for specified categories. Here, "99999" indicates that the median and confidence interval was not reached due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: months				
median (confidence interval 95%)				
Coughing score	18.1 (7.2 to 99999)	16.6 (3.3 to 16.6)		
Dyspnoea score	4.1 (1.4 to 11.3)	3.3 (1.0 to 99999)		
Pain in chest score	99999 (11.1 to 99999)	99999 (1.6 to 99999)		
Pain in arm or shoulder score	12.5 (7.4 to 99999)	1.9 (1.6 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for C-ITT Population

End point title	Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for C-ITT Population

End point description:

TTD in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for symptoms domains (or decrease for functioning domains from baseline for cough, dyspnea [single item and multi-item scales] chest pain [single item], pain in arm/shoulder and fatigue as measured by the EORTC QLQ-LC13. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). "n" indicates the number of subjects evaluated for specified categories. Here, "99999" indicates that the median and confidence interval was not reached

due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: months				
median (confidence interval 95%)				
Coughing score	99999 (8.3 to 99999)	16.6 (1.2 to 16.6)		
Dyspnoea score	9.7 (1.5 to 14.4)	1.4 (0.8 to 99999)		
Pain in chest score	99999 (9.7 to 99999)	99999 (1.4 to 99999)		
Pain in arm or shoulder score	11.1 (4.1 to 99999)	1.7 (0.9 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for ITT Population

End point title	Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for ITT Population

End point description:

TTD in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for symptoms domains (or decrease for functioning domains from baseline for cough, dyspnea [single item and multi-item scales] chest pain [single item], pain in arm/shoulder and fatigue as measured by the EORTC QLQ-C30. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. Here, "99999" indicates that the median and upper limit of confidence interval was not reached because of less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: months				
median (confidence interval 95%)				
Dyspnoea score	13.3 (2.9 to 99999)	8.3 (1.2 to 8.3)		
Fatigue score	5.6 (1.4 to 99999)	1.2 (0.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for C-ITT Population

End point title	Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for C-ITT Population

End point description:

TTD in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for symptoms domains (or decrease for functioning domains from baseline for cough, dyspnea [single item and multi-item scales] chest pain [single item], pain in arm/shoulder and fatigue as measured by the EORTC QLQ-C30. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). Here, "99999" indicates that the median and upper limit of confidence interval was not reached because of less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	26		
Units: months				
median (confidence interval 95%)				
Dyspnoea score	16.6 (2.9 to 99999)	8.3 (1.0 to 8.3)		
Fatigue score	14.4 (2.6 to 99999)	1.0 (0.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for C-ITT Population

End point title	TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for C-ITT Population

End point description:

TTD for a composite of three symptoms (cough, dyspnea, chest pain) in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for any component of the composite of the three following symptoms [cough, dyspnea [multi-item subscales QLQ-LC13] and chest pain]) as measured by the EORTC QLQ-LC13. C-ITT included subjects in ITT population with CNS metastasis at baseline (as per IRC assessment). Here, "99999" indicates that the upper limit of confidence interval was not reached due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: months				
median (confidence interval 95%)	2.8 (0.9 to 5.6)	1.4 (0.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for ITT Population

End point title	TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for ITT Population

End point description:

TTD for a composite of three symptoms (cough, dyspnea, chest pain) in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for any component of the composite of the three following symptoms [cough, dyspnea [multi-item subscales QLQ-LC13] and chest pain]) as measured by the EORTC QLQ-LC13. ITT population included all subjects randomised in the study, irrespective of whether or not they received study drug. Here, "99999" indicates that the upper limit of confidence interval was not reached due to less number of subjects with the event.

End point type	Secondary

End point timeframe:

Approximately 15 months (baseline, Weeks 3, 6, 12 and every 6 weeks until PD, death, or withdrawal from study prior to PD)

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	40		
Units: months				
median (confidence interval 95%)	1.4 (0.9 to 4.2)	1.4 (0.9 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety (SAF) population included all subjects who received at least one dose of any study drug.

End point type	Secondary

End point timeframe:

Approximately 15 months

End point values	Experimental: Alectinib	Active Comparator: Premetrexed/Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	34		
Units: percentage of subjects				
number (not applicable)	89.6	89.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 15 months

Adverse event reporting additional description:

SAF population included all subjects who received at least one dose of any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Active Comparator: Premetrexed/Docetaxel

Reporting group description:

Participants received chemotherapy with either pemetrexed (500 milligrams per square meter [mg/m^2] of body surface area) or docetaxel (75 mg/m^2) intravenously.

Reporting group title	Experimental: Alectinib

Reporting group description:

Participants received oral alectinib at a dose of 600 milligrams (mg) twice daily, taken with food and treatment discontinued until disease progression, unacceptable toxicity, withdrawal of consent or death.

Serious adverse events	Active Comparator: Premetrexed/Docetaxel	Experimental: Alectinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)	20 / 77 (25.97%)	
number of deaths (all causes)	4	26	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
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			
Death			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			

subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar ataxia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (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 / 37 (5.41%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 37 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Comparator: Premetrexed/Docetaxel	Experimental: Alectinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 37 (67.57%)	36 / 77 (46.75%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 37 (0.00%)	6 / 77 (7.79%)	
occurrences (all)	0	8	
Blood creatinine increased			
subjects affected / exposed	0 / 37 (0.00%)	5 / 77 (6.49%)	
occurrences (all)	0	7	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 37 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	4	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	3 / 77 (3.90%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	3 / 37 (8.11%)	5 / 77 (6.49%)	
occurrences (all)	3	6	
Neuropathy peripheral			
subjects affected / exposed	2 / 37 (5.41%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Paraesthesia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 37 (10.81%)	12 / 77 (15.58%)	
occurrences (all)	4	12	
Neutropenia			
subjects affected / exposed	4 / 37 (10.81%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 37 (16.22%)	9 / 77 (11.69%)	
occurrences (all)	6	14	
Fatigue			
subjects affected / exposed	9 / 37 (24.32%)	5 / 77 (6.49%)	
occurrences (all)	10	7	
Oedema peripheral			
subjects affected / exposed	2 / 37 (5.41%)	11 / 77 (14.29%)	
occurrences (all)	2	11	
Pyrexia			
subjects affected / exposed	3 / 37 (8.11%)	3 / 77 (3.90%)	
occurrences (all)	5	4	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 37 (5.41%)	2 / 77 (2.60%)	
occurrences (all)	2	2	

Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	2 / 37 (5.41%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 37 (10.81%)	16 / 77 (20.78%)	
occurrences (all)	5	21	
Vomiting			
subjects affected / exposed	2 / 37 (5.41%)	3 / 77 (3.90%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	6 / 37 (16.22%)	3 / 77 (3.90%)	
occurrences (all)	8	4	
Diarrhoea			
subjects affected / exposed	2 / 37 (5.41%)	5 / 77 (6.49%)	
occurrences (all)	3	6	
Abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	5 / 77 (6.49%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 37 (10.81%)	8 / 77 (10.39%)	
occurrences (all)	5	9	
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	9 / 77 (11.69%)	
occurrences (all)	0	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 37 (21.62%)	1 / 77 (1.30%)	
occurrences (all)	8	1	
Pruritus generalised			
subjects affected / exposed	3 / 37 (8.11%)	0 / 77 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 37 (5.41%)	10 / 77 (12.99%)	
occurrences (all)	2	10	
Myalgia			
subjects affected / exposed	4 / 37 (10.81%)	11 / 77 (14.29%)	
occurrences (all)	5	12	
Pain in extremity			
subjects affected / exposed	2 / 37 (5.41%)	2 / 77 (2.60%)	
occurrences (all)	2	2	
Arthralgia			
subjects affected / exposed	3 / 37 (8.11%)	4 / 77 (5.19%)	
occurrences (all)	3	6	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)	2 / 77 (2.60%)	
occurrences (all)	2	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	5 / 77 (6.49%)	
occurrences (all)	1	5	
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	6 / 77 (7.79%)	
occurrences (all)	0	7	
Nasopharyngitis			
subjects affected / exposed	1 / 37 (2.70%)	4 / 77 (5.19%)	
occurrences (all)	1	5	
Upper respiratory tract infection			
subjects affected / exposed	1 / 37 (2.70%)	7 / 77 (9.09%)	
occurrences (all)	1	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 37 (10.81%)	7 / 77 (9.09%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2015	• Throughout the protocol, a clarification for the timing of first administration of pemetrexed was added, indicating that required premedication for premetrexed administration (and not the study drug itself) was to be started as soon as possible after randomisation; subsequent treatment with study drug could be started according to local practice. In addition the time frame indicated for starting required premedication was changed, and a referral to local practice was added • For the subject-reported outcome (PRO) analysis of TTD, description of the analyses was aligned within the protocol in order to specify the lung cancer symptoms that were to be analyzed. In addition, description of the composite endpoint of three lung cancer symptoms was aligned within the protocol. The rationale for analyzing TTD based on the specified lung cancer symptoms and the composite endpoint was that these were used in the PROFILE 1007 trial, comparing the PRO outcome for subjects receiving crizotinib with subjects receiving chemotherapy. In addition, the symptoms that were to be analyzed were aligned with what was to be observed in the Phase III NCT02075840 ALEX trial • Docetaxel, was updated in order to emphasize that administration of required premedication was to be started as soon as possible after randomisation, followed by administration of docetaxel as per local practice • Description of study was updated to clarify the treatment duration of subjects on either of the two treatment arms, emphasizing that for entering the post progression treatment period (PPTP), receiving either alectinib cross over treatment or treatment beyond progression, a radiological, RECIST v.1.1 based disease progression needs to be documented and that subjects need to fulfill the safety based criteria for receiving alectinib. This needed clarification in order to prevent premature cross over from the chemotherapy arms, which would put the primary endpoint of the study (PFS as per investigator) at risk
26 November 2015	• Background section on alectinib was updated in order to reflect the most recent efficacy and safety results available from Phase II Studies NCT01871805 and NCT01801111 • Efficacy objectives and inclusion criterion number 2 was changed in order to further specify the subject population for the study. Subjects randomized to the trial had to have progressed on crizotinib or had developed intolerability to crizotinib treatment to be eligible for the trial. The two Phase II trials NCT01871805 and NCT01801111 were both conducted in crizotinib failed subjects. Future approval was to be in this setting, and the results from the current study was intended to support these data • For PRO measures, a sentence was added to indicate that the results from EORTC QOQ-C30, EORTC QLQ-LC13 and EQ-5D-5L questionnaires were analyzed in the overall subject group, as well as in the subgroup of subjects with CNS metastases. Due to the fact that at least 50% of the subject population recruited to the trial would have CNS metastases at baseline, it was important to look in particular at that subgroup to see if the efficacy results seen for this subject group also translated into increased quality of life with regards to general lung cancer symptoms • For the EORTC QLQ-BN20 analysis, in order to have a more detailed understanding of the treatment effect on the quality of life of subjects with CNS metastases, a third question chosen from the BN20 questionnaire was added in accordance with a recommendation from the Study Steering Committee • Inclusion criterion number 2 was updated in order to clarify that the two lines of prior NSCLC treatment required for subject to be eligible for the study needed to have been administered in the advanced or metastatic setting

26 November 2015	• Inclusion criterion number 12 was modified in order to clarify that not only within 3 days before first dose of study drug a negative pregnancy test be obtained, but also that the results had to be available prior to randomisation in order for the subject to be eligible • Description of Study was updated to clarify details on the PPTP of the trial to include subjects who cross over to receive alectinib upon progression on chemotherapy, and subjects who continue to receive alectinib in treatment beyond progression • Inclusion criterion number 13 was changed to reflect updated guidelines on contraception. For this, reference to double-barrier methods for contraception during the study was removed • Inclusion criterion number 14 was modified to emphasize that the requirement for men to use contraceptive method resulting in a failure rate of less than 1% per year during treatment with study drug and for at least 3 months after permanent discontinuation of study drug but for subjects receiving pemetrexed or docetaxel, local label should be referred to • Secondary Efficacy Endpoints were modified for the secondary endpoint of Time to CNS Progression. In the previous version of the protocol, it was indicated that this would be analyzed using a Kaplan-Meier(KM) estimate and a log-rank test. However due to the competing risks inherent to the analysis of this endpoint, where systemic progression acts as a competing risk for the CNS time to progression, HR and 95% CI and two-sided log-rank test were to be performed on the basis of cause-specific hazard functions was to be used instead to analyze Time to CNS progression. New language was also added to clarify the potential methods that were to be used for assessment of the impact of crossing over to alectinib
26 November 2015	• Safety Analysis section was updated to reflect that 95% CI was not to be displayed. Reference to the 95% CI was included in previous version of the protocol by error. In addition, new language was added to clarify potential assessments that were to be used to examine safety in subjects who cross over to alectinib following progression on chemotherapy or who continue treatment beyond progression on alectinib
20 May 2016	• Change in the risk of hepatobiliary laboratory tests elevations to hepatotoxicity for alectinib, based on following information: 2 subjects with Grade 3-4 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevations had documented drug-induced liver injury by liver biopsy in alectinib pivotal Phase II clinical trials (NCT01871805 and NCT01801111). Concurrent elevations in ALT or AST greater than or equal to three times the upper limit of normal (ULN) and total bilirubin greater than or equal to two times the ULN, with normal ALP, occurred in 1 subject treated in alectinib clinical trials • Change in the monitoring of liver function tests, with more intensive monitoring during the first 3 months of treatment. The majority of transaminase and bilirubin elevations (76% of the subjects with hepatic transaminase elevations and 68% of the subjects with bilirubin elevations) occurred during the first 3 months of treatment, and there were also events, including severe ones, with later onset. As such, monitoring had been intensified and measurements of liver function tests had been added at Weeks 2, 4, 8, 10, and 12 for subjects in the alectinib arm • Change in the risk of muscular AEs and creatine phosphokinase (CPK) elevations to severe myalgia and CPK elevations for alectinib, based on following information: Grade 3 myalgia and CPK elevations had been reported with alectinib treatment and were reversible upon dose reduction and interruption • Change in the monitoring of CPK, with more intensive monitoring during the first month of treatment (added Week 2 and Week 4 measurement of CPK for subjects in the alectinib arm) since median time to Grade 3 CPK elevation was 14 days (interquartile range: 13–14 days)
20 May 2016	• The list of AEs related to ALK inhibitors and alectinib data had been updated to align with the Investigator's Brochure, Version 6, and the addendum to the Investigator's Brochure, Version 6. The guideline for management of specific AEs with alectinib had been amended accordingly • Restriction related to concomitant medications known to prolong the QT interval was removed. The restriction was no longer required for alectinib-treated subjects based on the detailed evaluation of the pooled ECG data from the two pivotal studies NCT01871805 and NCT01801111, and ECG data from the supportive AF-001JP study, which showed no evidence of alectinib causing any clinically relevant QTcF prolongation. Further, there was no apparent correlation between the change in QTcF and alectinib plasma concentration. For docetaxel and pemetrexed, no such restrictions were required according to the corresponding labels

07 December 2016	• Sample size assumptions. The expected median time to PFS was increased from 6 months to 7 months on the alectinib arm (no change in the chemotherapy arm). This change was made because Phase II studies of alectinib in the crizotinib-failure setting had shown a consistent PFS outcome of 8.2–8.9 months, making the original 6-month assumption unrealistic. Consequently, assuming an accrual period of 12 months and a primary analysis with 50 PFS events planned after approximately 13 months, a sample size of 90 subjects (60 subjects in the experimental arm [alectinib] and 30 subjects in the control arm [chemotherapy]) provided 80% power to detect a significant improvement in the median time to PFS from 3 to 7 months (i.e., Hazard ratio [HR] of 0.43). With this new information on efficacy from Phase II studies and the resulting amendment of the NCT02604342 study, the same objective of superiority would be reached, with a smaller sample size and smaller target number of PFS events • Recruitment caps. Earlier versions of the NCT02604342 study protocol had a recruitment cap on the chemotherapy arm, such that 50% of subjects were to receive docetaxel and 50% were to receive pemetrexed. The current version of the protocol removed this constraint. This change was made because current standard of- care therapy in Europe in the front-line setting is a pemetrexed-based chemotherapy. Consequently, few subjects were available for enrollment who had not yet received pemetrexed, presenting a significant recruitment challenge. The change had the additional benefit of making the control arm in the study (chemotherapy) more directly analogous to a standard clinical population
07 December 2016	• ALK testing. The current version of the protocol no longer specified the exact type and catalog number of the fluorescence in situ hybridization (FISH) test or immunohistochemistry (IHC) test mandated for identification and inclusion of ALK-positive subjects. Instead, the acceptable tests were broadened to include any assays that were validated and in line with published national or international guidelines. This change was made because ALK testing is a routine test performed for selecting subjects eligible for crizotinib
01 December 2017	Reduction in the number of assessments and subject visits during follow-up due to the study having met its primary objective and because of a favorable safety profile; removal of the mandate for ongoing IRC review; post-treatment visit was changed from 3 months after the last administration of study drug to 4 weeks after the last administration in order to align more closely to other alectinib trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported