Clinical trial results:
Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced NonSmall Cell Lung Cancer

Summary

EudraCT number	2013-004133-33
Trial protocol	PL IT GB PT ES DE FR GR
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	23 February 2018
First version publication date	23 February 2018

Trial information

Trial identification

Sponsor protocol code	BO28984

Additional study identifiers

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

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	Medical Communications, 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	Interim
Date of interim/final analysis	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate and compare the efficacy of alectinib compared to crizotinib in patients with treatment-naive anaplastic lymphoma kinase (ALK)-positive advanced non−small cell lung cancer (NSCLC), 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	19 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	China: 10
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Costa Rica: 3
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Guatemala: 1
Country: Number of subjects enrolled	Hong Kong: 19
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Korea, Republic of: 48
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Poland: 13

Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Thailand: 19
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Taiwan: 14
Worldwide total number of subjects	303
EEA total number of subjects	62

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)	233
From 65 to 84 years	68
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study recruited treatment-naive subjects with Anaplastic Lymphoma Kinase (ALK)-positive advanced Non-Small Cell Lung Cancer (NSCLC) in 29 countries from August 2014 to January 2016.

Pre-assignment

Screening details:

A total of 303 subjects were randomized at the time of clinical cut-off (CCO) date and included in the intent-to-treat (ITT) population; 152 participants in the alectinib arm and 151 participants in the crizotinib 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 alectinib at 600 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.

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

Dosage and administration details:

Subjects received alectinib at 600 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.

Arm title	Comparator: Crizotinib

Arm description:

Subjects received crizotinib at 250 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.

Arm type	Active comparator
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received crizotinib at 250 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.

Number of subjects in period 1	Experimental: Alectinib	Comparator: Crizotinib
Started	152	151
Completed	0	0
Not completed	152	151
Consent withdrawn by subject	13	22
Physician decision	1	3
Adverse event, non-fatal	-	2
Death	35	40
Ongoing at CCOD	99	82
Reason not specified	1	-
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Alectinib
Reporting group description:	
Subjects received alectinib at 600 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	
Reporting group title	Comparator: Crizotinib
Reporting group description:	
Subjects received crizotinib at 250 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	

Reporting group values	Experimental: Alectinib	Comparator: Crizotinib	Total
Number of subjects	152	151	303
Age categorical Units: Subjects			
<65	115	118	233
>=65	37	33	70
Age Continuous Units: years			
arithmetic mean	56.3	53.8	
standard deviation	± 12.0	± 13.5	-
Sex: Female, Male Units: Subjects			
Female	84	87	171
Male	68	64	132
Race/Ethnicity, Customized Units: Subjects			
Ethnicity - Hispanic or Latino|	8	8	16
Ethinicity - Not Hispanic or Latino|	138	136	274
Ethnicity - Not Stated|	6	7	13
Race/Ethnicity, Customized Units: Subjects			
Race - American Indian or Alaska Native|	4	0	4
Race - Asian|	69	69	138
Race - Black or African American|	0	4	4
Race - Native Hawaiian or other Pacific Islander|	1	1	2
Race - White|	76	75	151
Race - Unknown|	2	2	4

End points

End points reporting groups

Reporting group title	Experimental: Alectinib
Reporting group description:	
Subjects received alectinib at 600 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	
Reporting group title	Comparator: Crizotinib
Reporting group description:	
Subjects received crizotinib at 250 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	

Primary: Progression-Free Survival (PFS) by Investigator Assessment

End point title	Progression-Free Survival (PFS) by Investigator Assessment
End point description:	
PFS was assessed as time to disease progression or death whichever occurred first by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. 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. 99999 = The value is not available because it had not been reached at the time of data cutoff date (9 Feb 2017).	
End point type	Primary
End point timeframe:	
Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)	

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: months				
median (confidence interval 95%)	99999 (17.7 to 99999)	11.1 (9.1 to 13.1)		

Statistical analyses

Statistical analysis title	PFS by Investigator
Statistical analysis description:	
Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by Investigator.	
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib

Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard Ratio, stratified
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.65

Primary: Percentage of Participants with PFS event by Investigator assessment

End point title	Percentage of Participants with PFS event by Investigator assessment[1]

End point description:

PFS was assessed percentage of participants with disease progression or death whichever occurred first by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. 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.

End point type	Primary

End point timeframe:

Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported.

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (not applicable)	40.8	67.5		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Independent Review Committee (IRC)-assessed

End point title	PFS Independent Review Committee (IRC)-assessed

End point description:

PFS was assessed as time to disease progression or death whichever occurred first by IRC assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. 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.
99999 = The value is not available because it had not been reached at the time of data cutoff date (9

Feb 2017).

End point type	Secondary

End point timeframe:

Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: months				
median (confidence interval 95%)	25.7 (19.9 to 99999)	10.4 (7.7 to 14.6)		

Statistical analyses

Statistical analysis title	PFS by IRC

Statistical analysis description:

Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.

Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.7

Secondary: Percentage of Participants with Central Nervous System (CNS) Progression as Determined by IRC Using RECIST V1.1 Criteria.

End point title	Percentage of Participants with Central Nervous System (CNS) Progression as Determined by IRC Using RECIST V1.1 Criteria.

End point description:

Time to CNS progression was assessed as percentage of participants with event defined as time from randomization until first radiographic evidence of CNS progression by IRC. The risk for a CNS progression without a prior non-CNS progression with alectinib compared with crizotinib.

End point type	Secondary

End point timeframe:

Randomization to the first occurrence of disease progression in the CNS (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (not applicable)	11.8	45.0		

Statistical analyses

Statistical analysis title	CNS progression by IRC using RECIST v1.1
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Cause-Specific Hazard Ratio
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.28

Notes:

[2] - IRC, RECIST v1.1 Stratified Analysis (by race (Asian vs non-Asian) and CNS metastases at baseline by IRC)

Secondary: Percentage of Participants With Objective Response Rate (ORR) of Complete Response (CR) or Partial Response (PR) as Determined by The Investigators According to RECIST V1.1 Criteria

End point title	Percentage of Participants With Objective Response Rate (ORR) of Complete Response (CR) or Partial Response (PR) as Determined by The Investigators According to RECIST V1.1 Criteria

End point description:

ORR was defined as the percentage of participants 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.

End point type	Secondary

End point timeframe:

Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (confidence interval 95%)	82.9 (75.95 to 88.51)	75.5 (67.84 to 82.12)		

Statistical analyses

Statistical analysis title	ORR by Investigator using RECIST v1.1
Statistical analysis description: Stratified analysis	
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0936
Method	Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	16.5

Secondary: Duration of Response (DOR) According to RECIST V1.1 Criteria as assessed by the Investigators

End point title	Duration of Response (DOR) According to RECIST V1.1 Criteria as assessed by the Investigators

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 participants who had a best overall response (BOR) of CR or PR.
99999 = The value is not available because it had not been reached at the time of data cutoff date (9 Feb 2017).

End point type	Secondary

End point timeframe:

First occurrence of objective response to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	114		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	11.1 (7.9 to 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was defined as the time from randomization to death from any cause.
99999 = The value is not available because it had not been reached at the time of data cutoff date (9 Feb 2017).

End point type	Secondary

End point timeframe:

From randomization until death (up to 43 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Stratified analysis
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2405
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.2

Secondary: Percentage of Participants with CNS ORR of CR or PR IRC-assessed According to RECIST v1.1 criteria

End point title	Percentage of Participants with CNS ORR of CR or PR IRC-assessed According to RECIST v1.1 criteria

End point description:

CNS ORR was defined as the percentage of participants who attained CR or PR and had measurable CNS lesions at baseline. 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.

End point type	Secondary

End point timeframe:

Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (confidence interval 95%)				
Measurable CNS lesions at baseline N=21,22	81.0 (58.09 to 94.55)	50.0 (28.22 to 71.78)		
Measurable and non-measurable CNS lesions N=64,58	59.4 (46.37 to 71.49)	25.9 (15.26 to 39.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: CNS DOR IRC-assessed according to RECIST v1.1 criteria

End point title	CNS DOR IRC-assessed according to RECIST v1.1 criteria

End point description:

CNS 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 participants who had a best overall response (BOR) of CR or PR.
99999 = The value is not available because it had not been reached at the time of data cutoff date (9 Feb 2017).

End point type	Secondary

End point timeframe:

First occurrence of CNS objective response to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	22		
Units: months				
median (confidence interval 95%)	17.3 (14.8 to 99999)	5.5 (2.1 to 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

An adverse event (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.

End point type	Secondary

End point timeframe:

Baseline up to 28 months in the crizotinib arm and up to 30 months in the alectinib arm

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (not applicable)	97.0	97.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve (AUC) of Alectinib

End point title	Area Under The Concentration-Time Curve (AUC) of Alectinib[3]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib) (baseline), 1, 2, 4, 6, and 8 hours post-dose at Visit 0 (first dosing day) and Week 4; Pre-dose (within 2 hours) at Week 8, then every 8 weeks until disease progression or death/withdrawal (up to 33 months)

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: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline (n=10)	713 (± 104.9)			
Treatment - week 4 (n=9)	5030 (± 47.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Alectinib

End point title	Maximum Concentration (Cmax) of Alectinib[4]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)

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: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Baseline (n=10)	211 (± 55.5)			
Treatment - week 4 (n=9)	717 (± 46.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (tmax) of Alectinib

End point title	Time to Reach Cmax (tmax) of Alectinib[5]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4;

Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: hours				
median (full range (min-max))				
Baseline (n=10)	6.03 (1.98 to 12.00)			
Treatment - week 4 (n=9)	4.02 (2.00 to 8.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of Alectinib Metabolite

End point title	AUC of Alectinib Metabolite[6]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib) (baseline), 1, 2, 4, 6, and 8 hours post-dose at Visit 0 (first dosing day) and Week 4; Pre-dose (within 2 hours) at Week 8, then every 8 weeks until disease progression or death/withdrawal (up to 33 months)

Notes:

[6] - 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: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline (n=10)	142 (± 191.7)			
Treatment - week 4 (n=9)	2230 (± 37.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Alectinib Metabolite

End point title	Cmax of Alectinib Metabolite[7]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)

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: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Baseline (n=10)	56.2 (± 80.1)			
Treatment - week 4 (n=9)	321 (± 32.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: tmax of Alectinib Metabolite

End point title	tmax of Alectinib Metabolite[8]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were collected and analyzed for the reported arm only.

End point values	Experimental: Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: hours				
median (full range (min-max))				
Baseline (n=10)	8.00 (5.98 to 12.00)			
Treatment - week 4 (n=9)	6.00 (2.00 to 10.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration by European Organization for The Research And Treatment of Cancer (EORTC) Quality Of Life Questionnaire Core 30 (C30)

End point title	Time to Deterioration by European Organization for The Research And Treatment of Cancer (EORTC) Quality Of Life Questionnaire Core 30 (C30)

End point description:

The EORTC QLQ-30 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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.
99999=not reached at CCOD

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: months				
median (confidence interval 95%)				
Fatigue	99999 (99999 to 99999)	99999 (9.4 to 99999)		
Dyspnea	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Fatigue
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2079
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.19

Statistical analysis title	Dyspnea
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1137
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	3.15

Secondary: Time to Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13)

End point title	Time to Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13)

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: months				
median (confidence interval 95%)				
Coughing	99999 (24.0 to 99999)	99999 (-99999 to 99999)		
Dyspnoea	22.8 (11.8 to 99999)	99999 (21.0 to 99999)		

Pain in arm and shoulder	99999 (-99999 to 99999)	99999 (-99999 to 99999)		
Pain in chest	99999 (-99999 to 99999)	99999 (-99999 to 99999)		
Composite score (c, p in c, d)	12.7 (5.0 to 99999)	21.0 (9.8 to 99999)		

Statistical analyses

Statistical analysis title	Coughing
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7042
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.74

Statistical analysis title	Dyspnea
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0285
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.92

Statistical analysis title	Pain in arm and shoulder
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib

Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2377
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.61

Statistical analysis title	Pain in chest
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0796
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.1

Statistical analysis title	Cmposite score
Comparison groups	Experimental: Alectinib v Comparator: Crizotinib
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6435
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.68

Secondary: Health-Related Quality of Life (HRQoL) by EORTC Quality of Life

Questionnaire C30 Score Global Health Status

End point title	Health-Related Quality of Life (HRQoL) by EORTC Quality of Life Questionnaire C30 Score Global Health Status

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Score on a scale				
median (full range (min-max))				
Baseline (n=100, 97)	66.67 (8.3 to 100.0)	66.67 (0.0 to 100.0)		
Treatment - week 4 (n=95, 89)	66.67 (0.0 to 100.0)	66.67 (16.7 to 100.0)		
Treatment - week 8 (n=89, 84)	75.0 (16.7 to 100.0)	75.0 (16.7 to 100.0)		
Treatment - week 12 (n=75, 78)	75.0 (25.0 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 16 (n=79, 73)	75.0 (16.7 to 100.0)	83.33 (16.7 to 100.0)		
Treatment - week 20 (n=73, 67)	75.0 (16.7 to 100.0)	75.0 (16.7 to 100.0)		
Treatment - week 24 (n=77, 71)	75.0 (16.7 to 100.0)	83.33 (8.3 to 100.0)		
Treatment - week 28 (n=67, 62)	75.0 (33.3 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 32 (n=73, 65)	75.0 (33.3 to 100.0)	66.67 (8.3 to 100.0)		
Treatment - week 36 (n=64, 61)	79.17 (16.7 to 100.0)	66.67 (16.7 to 100.0)		
Treatment - week 40 (n=74, 50)	75.0 (16.7 to 100.0)	83.33 (33.3 to 100.0)		
Treatment - week 44 (n=62, 47)	83.33 (16.7 to 100.0)	83.33 (16.7 to 100.0)		
Treatment - week 48 (n=67, 47)	66.67 (25.0 to 100.0)	83.33 (41.7 to 100.0)		
Treatment - week 52 (n=58, 44)	83.33 (16.7 to 100.0)	75.00 (41.7 to 100.0)		
Treatment - week 56 (n=61, 48)	75.0 (16.7 to 100.0)	75.0 (41.7 to 100.0)		
Treatment - week 60 (n=47, 39)	75.0 (33.3 to 100.0)	75.0 (50.0 to 100.0)		
Treatment - week 64 (n=55, 39)	75.0 (33.3 to 100.0)	83.33 (41.7 to 100.0)		
Treatment - week 68 (n=49, 34)	75.0 (33.3 to 100.0)	79.17 (33.3 to 100.0)		

Treatment - week 72 (n=54, 34)	75.0 (33.3 to 100.0)	75.00 (8.3 to 100.0)		
Treatment - week 76 (n=42, 29)	75.0 (41.7 to 100.0)	75.0 (16.7 to 100.0)		
Treatment - week 80 (n=43, 23)	75.0 (33.3 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 84 (n=33, 19)	83.33 (41.7 to 100.0)	66.67 (33.3 to 100.0)		
Treatment - week 88 (n=36, 16)	75.0 (33.3 to 100.0)	66.67 (33.3 to 100.0)		
Treatment - week 92 (n=30, 13)	70.83 (33.3 to 100.0)	75.0 (50.0 to 100.0)		
Treatment - week 96 (n=22, 11)	66.67 (33.3 to 100.0)	66.67 (33.3 to 100.0)		
Treatment - week 100 (n=18, 10)	66.67 (25.0 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 104 (n=15, 7)	66.67 (50.0 to 100.0)	66.67 (50.0 to 100.0)		
Treatment - week 108 (n=11, 7)	66.67 (50.0 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 112 (n=9, 4)	75.0 (50.0 to 100.0)	75.0 (33.3 to 100.0)		
Treatment - week 116 (n=4, 2)	70.83 (41.7 to 100.0)	91.67 (83.3 to 100.0)		
Treatment - week 120 (n=3, 0)	83.3 (50.0 to 100.0)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL by EORTC Quality of Life Questionnaire LC13 Score Coughing

End point title	HRQoL by EORTC Quality of Life Questionnaire LC13 Score Coughing

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Score on a scale				
median (full range (min-max))				
Baseline (n=100, 96)	33.33 (0.0 to 100.0)	33.33 (0.0 to 100.0)		

Treatment - week 4 (n=95, 89)	33.33 (0.0 to 100.0)	33.33 (0.0 to 100.0)		
Treatment - week 8 (n=89, 84)	33.33 (0.0 to 66.7)	33.33 (0.0 to 100.0)		
Treatment - week 12 (n=75, 78)	33.33 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - week 16 (n=79, 73)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - week 20 (n=73, 67)	33.33 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - week 24 (n=77, 71)	33.33 (0.0 to 100.0)	33.33 (0.0 to 100.0)		
Treatment - week 28 (n=67, 62)	33.33 (0.0 to 100.0)	16.67 (0.0 to 100.0)		
Treatment - week 32 (n=73, 65)	33.33 (0.0 to 100.0)	33.33 (0.0 to 100.0)		
Treatment - week 36 (n=64, 61)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - week 40 (n=74, 50)	33.33 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 44 (n=62, 47)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 48 (n=67, 47)	33.33 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 52 (n=58, 44)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - week 56 (n=61, 48)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - week 60 (n=47, 39)	33.33 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - week 64 (n=55, 39)	33.33 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 68 (n=49, 34)	33.33 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 72 (n=54, 34)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 76 (n=42, 29)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 80 (n=43, 23)	33.33 (0.0 to 66.7)	0.0 (0.0 to 33.33)		
Treatment - week 84 (n=33, 19)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.33)		
Treatment - week 88 (n=36, 16)	33.33 (0.0 to 100.0)	0.0 (0.0 to 33.33)		
Treatment - week 92 (n=30, 13)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - week 96 (n=22, 11)	16.67 (0.0 to 66.7)	0.0 (0.0 to 33.33)		
Treatment - week 100 (n=18, 10)	0.0 (0.0 to 100.0)	0.0 (0.0 to 33.3)		
Treatment - week 104 (n=15, 7)	33.33 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - week 108 (n=11, 7)	33.33 (0.0 to 66.7)	33.33 (0.0 to 33.33)		
Treatment - week 112 (n=9, 4)	33.33 (0.0 to 33.33)	0.0 (0.0 to 33.33)		
Treatment - week 116 (n=4, 2)	33.33 (0.0 to 33.33)	16.67 (0.0 to 33.33)		
Treatment - week 120 (n=3, 0)	33.33 (33.33 to 33.33)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL by EORTC Quality of Life Questionnaire LC13 Score Dyspnoea

End point title	HRQoL by EORTC Quality of Life Questionnaire LC13 Score Dyspnoea

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Score on a scale				
median (full range (min-max))				
Baseline (n=100, 96)	22.22 (0.0 to 100.0)	22.22 (0.0 to 100.0)		
Treatment - Week 4 (n=95, 89)	22.22 (0.0 to 100.0)	22.22 (0.0 to 88.9)		
Treatment - Week 8 (n=89, 84)	22.22 (0.0 to 66.7)	11.11 (0.0 to 66.7)		
Treatment - Week 12 (n=75, 78)	22.22 (0.0 to 66.7)	11.11 (0.0 to 66.7)		
Treatment - Week 16 (n=79, 73)	22.22 (0.0 to 77.8)	11.11 (0.0 to 88.9)		
Treatment - Week 20 (n=73, 67)	22.22 (0.0 to 88.9)	11.11 (0.0 to 66.7)		
Treatment - Week 24 (n=77, 71)	22.22 (0.0 to 77.8)	11.11 (0.0 to 77.8)		
Treatment - Week 28 (n=67, 62)	11.11 (0.0 to 44.4)	11.11 (0.0 to 100.0)		
Treatment - Week 32 (n=73, 65)	22.22 (0.0 to 66.7)	11.11 (0.0 to 88.9)		
Treatment - Week 36 (n=64, 61)	16.67 (0.0 to 77.8)	11.11 (0.0 to 66.7)		
Treatment - Week 40 (n=74, 50)	11.11 (0.0 to 55.6)	5.56 (0.0 to 66.7)		
Treatment - Week 44 (n=62, 47)	11.11 (0.0 to 88.9)	11.11 (0.0 to 77.8)		

Treatment - Week 48 (n=67, 47)	22.22 (0.0 to 55.6)	11.11 (0.0 to 44.4)		
Treatment - Week 52 (n=58, 44)	22.22 (0.0 to 44.4)	11.11 (0.0 to 66.7)		
Treatment - Week 56 (n=61, 48)	22.22 (0.0 to 77.8)	11.11 (0.0 to 77.8)		
Treatment - Week 60 (n=47, 39)	22.22 (0.0 to 77.8)	0.0 (0.0 to 55.6)		
Treatment - Week 64 (n=55, 39)	22.22 (0.0 to 66.7)	11.11 (0.0 to 66.7)		
Treatment - Week 68 (n=49, 34)	22.22 (0.0 to 77.8)	11.11 (0.0 to 55.6)		
Treatment - Week 72 (n=54, 34)	22.22 (0.0 to 66.7)	11.11 (0.0 to 44.4)		
Treatment - Week 76 (n=42, 29)	11.11 (0.0 to 66.7)	11.11 (0.0 to 55.6)		
Treatment - Week 80 (n=43, 23)	22.22 (0.0 to 66.7)	11.11 (0.0 to 55.6)		
Treatment - Week 84 (n=33, 19)	11.11 (0.0 to 66.7)	11.11 (0.0 to 44.4)		
Treatment - Week 88 (n=36, 16)	22.22 (0.0 to 55.6)	22.22 (0.0 to 33.3)		
Treatment - Week 92 (n=30, 13)	22.22 (0.0 to 44.4)	22.22 (0.0 to 77.8)		
Treatment - Week 96 (n=22, 11)	22.22 (0.0 to 66.7)	22.22 (0.0 to 44.4)		
Treatment - Week 100 (n=18, 10)	22.22 (0.0 to 55.6)	27.78 (0.0 to 44.4)		
Treatment - Week 104 (n=15, 7)	11.11 (0.0 to 66.7)	11.11 (0.0 to 33.3)		
Treatment - Week 108 (n=11, 7)	22.22 (0.0 to 66.7)	11.11 (0.0 to 33.3)		
Treatment - Week 112 (n=9, 4)	11.11 (11.11 to 44.4)	27.78 (0.0 to 33.3)		
Treatment - Week 116 (n=4, 2)	16.67 (11.1 to 22.2)	16.67 (0.0 to 33.3)		
Treatment - Week 120 (n=3, 0)	22.22 (11.1 to 33.3)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Chest

End point title	HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Chest

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Score on a scale				
median (full range (min-max))				
Baseline (n=100, 96)	33.33 (0.0 to 100.0)	0.0 (0.0 to 100.0)		
Treatment - Week 4 (n=95, 89)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 8 (n=89, 84)	0.0 (0.0 to 33.3)	0.0 (0.0 to 66.7)		
Treatment - Week 12 (n=75, 78)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 16 (n=79, 73)	0.0 (0.0 to 33.3)	0.0 (0.0 to 66.7)		
Treatment - Week 20 (n=73, 67)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 24 (n=77, 71)	0.0 (0.0 to 33.3)	0.0 (0.0 to 66.7)		
Treatment - Week 28 (n=67, 62)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 32 (n=73, 65)	0.00 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 36 (n=64, 61)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 40 (n=74, 50)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 44 (n=62, 47)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - Week 48 (n=67, 47)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 52 (n=58, 44)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 56 (n=61, 48)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 60 (n=47, 39)	0.0 (0.0 to 33.3)	0.0 (0.0 to 66.7)		
Treatment - Week 64 (n=55, 39)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 68 (n=49, 34)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 72 (n=54, 34)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 76 (n=42, 29)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 80 (n=43, 23)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 84 (n=33, 19)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 88 (n=36, 16)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 92 (n=30, 13)	0.0 (0.0 to 33.3)	0.0 (0.0 to 33.3)		
Treatment - Week 96 (n=22, 11)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		

Treatment - Week 100 (n=18, 10)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 104 (n=15, 7)	33.33 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 108 (n=11, 7)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 112 (n=9, 4)	0.0 (0.0 to 66.7)	16.67 (0.0 to 33.3)		
Treatment - Week 116 (n=4, 2)	0.0 (0.0 to 33.3)	16.67 (0.0 to 33.3)		
Treatment - Week 120 (n=3, 0)	0.0 (0.0 to 66.7)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Arm and Shoulder

End point title	HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Arm and Shoulder

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Score on a scale				
median (full range (min-max))				
Baseline (n=100, 96)	0.0 (0.0 to 100.0)	0.0 (0.0 to 100.0)		
Treatment - Week 4 (n=95, 89)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - Week 8 (n=89, 84)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - Week 12 (n=75, 78)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - Week 16 (n=79, 73)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 20 (n=73, 67)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 24 (n=77, 71)	0.0 (0.0 to 33.3)	0.0 (0.0 to 66.7)		
Treatment - Week 28 (n=67, 62)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		

Treatment - Week 32 (n=73, 65)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - Week 36 (n=64, 61)	0.0 (0.0 to 100.0)	0.0 (0.0 to 66.7)		
Treatment - Week 40 (n=74, 50)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - Week 44 (n=62, 47)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - Week 48 (n=67, 47)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 52 (n=58, 44)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 56 (n=61, 48)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 60 (n=47, 39)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 64 (n=55, 39)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 68 (n=49, 34)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 72 (n=54, 34)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 76 (n=42, 29)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 80 (n=43, 23)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 84 (n=33, 19)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 88 (n=36, 16)	0.0 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 92 (n=30, 13)	0.0 (0.0 to 66.7)	0.0 (0.0 to 100.0)		
Treatment - Week 96 (n=22, 11)	33.33 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 100 (n=18, 10)	33.33 (0.0 to 66.7)	0.0 (0.0 to 66.7)		
Treatment - Week 104 (n=15, 7)	33.33 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 108 (n=11, 7)	0.0 (0.0 to 66.7)	0.0 (0.0 to 33.3)		
Treatment - Week 112 (n=9, 4)	0.0 (0.0 to 66.7)	16.67 (0.0 to 33.33)		
Treatment - Week 116 (n=4, 2)	16.67 (0.0 to 33.33)	16.67 (0.0 to 33.33)		
Treatment - Week 120 (n=3, 0)	33.33 (33.33 to 33.33)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PFS event by IRC

End point title	Percentage of Participants with PFS event by IRC

End point description:

PFS was assessed as percentage of participants with disease progression or death whichever occurred first by IRC assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. 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.

End point type	Secondary

End point timeframe:

Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of Participants				
number (not applicable)	41.4	60.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Central Nervous System (CNS) Progression as Determined by IRC Using Revised Assessment in Neuro Oncology (RANO) Criteria

End point title	Percentage of Participants with Central Nervous System (CNS) Progression as Determined by IRC Using Revised Assessment in Neuro Oncology (RANO) Criteria

End point description:

CNS progression was assessed as percentage of participants with event defined as time from randomization until first radiographic evidence of CNS progression by IRC. The risk for a CNS progression without a prior non-CNS progression with alectinib compared with crizotinib.

End point type	Secondary

End point timeframe:

Randomization to the first occurrence of disease progression in the CNS (assessed every 8 weeks up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of participants				
number (not applicable)	10.5	35.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with OS event

End point title	Percentage of Participants with OS event

End point description:

Overall survival (OS) was defined as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

From randomization until death (up to 43 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of participants				
number (not applicable)	23.0	26.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Deterioration by EORTC Quality Of Life Questionnaire Core 30 (C30)

End point title	Percentage of Participants with Deterioration by EORTC Quality Of Life Questionnaire Core 30 (C30)

End point description:

The EORTC QLQ-30 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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning. Confirmed clinically meaningful deterioration in global health status or function is defined as a >or=10-point decrease from baseline in a symptom score that must be held for at least two consecutive assessments or an initial >or=10-point decrease from baseline followed by death within 5 weeks from the last assessment.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of participants				
number (not applicable)				
Fatigue	21.7	25.2		
Dyspnea	17.1	9.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13)

End point title	Percentage of Participants with Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13)

End point description:

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. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning. Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a >or=10-point increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial >or=10-point increase above baseline followed by death within 5 weeks from the last assessment.

End point type	Secondary

End point timeframe:

Baseline, every 4 weeks until disease progression (up to 33 months)

End point values	Experimental: Alectinib	Comparator: Crizotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	151		
Units: Percentage of participants				
number (not applicable)				
Coughing	11	11		
Dyspnea	28	16		
Pain in arm and shoulder	18	12		
Pain in chest	7	11		
Composite score (c, p in c, d)	32	28		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 43 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Alectinib
Reporting group description:	
Subjects received alectinib at 600 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	
Reporting group title	Crizotinib
Reporting group description:	
Subjects received crizotinib at 250 mg orally BID from Visit 0 (baseline) until disease progression, unacceptable toxicity, withdrawal of consent or death.	

Serious adverse events	Alectinib	Crizotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 152 (28.95%)	45 / 151 (29.80%)	
number of deaths (all causes)	35	40	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian Cancer			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
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 / 152 (0.00%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			

subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
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			
Pyrexia			
subjects affected / exposed	1 / 152 (0.66%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia Malignant			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest Pain			

subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 152 (1.32%)	4 / 151 (2.65%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	2 / 152 (1.32%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 152 (1.32%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pulmonary Embolism			
subjects affected / exposed	2 / 152 (1.32%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopleural Fistula			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial Lung Disease			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 152 (0.66%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	2 / 152 (1.32%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 152 (0.66%)	4 / 151 (2.65%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human Chorionic Gonadotropin Increased			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			

subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Myocardial Infarction			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Bradycardia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
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	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			

subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 152 (1.32%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Vision Blurred			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 152 (0.00%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 152 (0.00%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Disorder			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug−Induced Liver Injury			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic Haematoma			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Impairment			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Kidney Injury			
subjects affected / exposed	4 / 152 (2.63%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 152 (3.29%)	4 / 151 (2.65%)	
occurrences causally related to treatment / all	2 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	3 / 152 (1.97%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 152 (1.32%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 152 (1.32%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Herpes Zoster			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter Infection			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Fasciitis			

subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal Candidiasis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Klebsiella			
subjects affected / exposed	0 / 152 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 152 (0.66%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alectinib	Crizotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	136 / 152 (89.47%)	140 / 151 (92.72%)	
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	26 / 152 (17.11%)	41 / 151 (27.15%)	
occurrences (all)	30	49	
Fatigue			
subjects affected / exposed	29 / 152 (19.08%)	25 / 151 (16.56%)	
occurrences (all)	34	25	
Asthenia			
subjects affected / exposed	11 / 152 (7.24%)	11 / 151 (7.28%)	
occurrences (all)	13	12	
Pyrexia			

subjects affected / exposed	7 / 152 (4.61%)	9 / 151 (5.96%)	
occurrences (all)	7	10	
Chest Pain			
subjects affected / exposed	9 / 152 (5.92%)	5 / 151 (3.31%)	
occurrences (all)	11	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 152 (7.24%)	9 / 151 (5.96%)	
occurrences (all)	16	11	
Dyspnoea			
subjects affected / exposed	8 / 152 (5.26%)	6 / 151 (3.97%)	
occurrences (all)	9	7	
Productive Cough			
subjects affected / exposed	8 / 152 (5.26%)	1 / 151 (0.66%)	
occurrences (all)	9	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 152 (9.87%)	9 / 151 (5.96%)	
occurrences (all)	15	9	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	22 / 152 (14.47%)	42 / 151 (27.81%)	
occurrences (all)	31	49	
Aspartate Aminotransferase Increased			
subjects affected / exposed	20 / 152 (13.16%)	37 / 151 (24.50%)	
occurrences (all)	30	46	
Blood Bilirubin Increased			
subjects affected / exposed	23 / 152 (15.13%)	2 / 151 (1.32%)	
occurrences (all)	25	2	
Blood Creatinine Increased			
subjects affected / exposed	11 / 152 (7.24%)	6 / 151 (3.97%)	
occurrences (all)	15	6	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	8 / 152 (5.26%)	7 / 151 (4.64%)	
occurrences (all)	10	10	

Weight Increased			
subjects affected / exposed	15 / 152 (9.87%)	0 / 151 (0.00%)	
occurrences (all)	15	0	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	6 / 152 (3.95%)	8 / 151 (5.30%)	
occurrences (all)	6	8	
Gamma−Glutamyltransferase Increased			
subjects affected / exposed	1 / 152 (0.66%)	10 / 151 (6.62%)	
occurrences (all)	1	11	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	8 / 152 (5.26%)	14 / 151 (9.27%)	
occurrences (all)	8	14	
Sinus Bradycardia			
subjects affected / exposed	8 / 152 (5.26%)	7 / 151 (4.64%)	
occurrences (all)	9	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 152 (2.63%)	29 / 151 (19.21%)	
occurrences (all)	4	33	
Dizziness			
subjects affected / exposed	12 / 152 (7.89%)	20 / 151 (13.25%)	
occurrences (all)	16	21	
Headache			
subjects affected / exposed	11 / 152 (7.24%)	13 / 151 (8.61%)	
occurrences (all)	12	16	
Paraesthesia			
subjects affected / exposed	3 / 152 (1.97%)	8 / 151 (5.30%)	
occurrences (all)	3	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 152 (19.08%)	7 / 151 (4.64%)	
occurrences (all)	34	7	
Neutropenia			
subjects affected / exposed	4 / 152 (2.63%)	11 / 151 (7.28%)	
occurrences (all)	4	24	

Eye disorders			
Visual Impairment			
subjects affected / exposed	2 / 152 (1.32%)	18 / 151 (11.92%)	
occurrences (all)	2	19	
Vision Blurred			
subjects affected / exposed	3 / 152 (1.97%)	10 / 151 (6.62%)	
occurrences (all)	3	11	
Photopsia			
subjects affected / exposed	0 / 152 (0.00%)	9 / 151 (5.96%)	
occurrences (all)	0	11	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	52 / 152 (34.21%)	49 / 151 (32.45%)	
occurrences (all)	61	53	
Nausea			
subjects affected / exposed	21 / 152 (13.82%)	70 / 151 (46.36%)	
occurrences (all)	23	83	
Diarrohea			
subjects affected / exposed	18 / 152 (11.84%)	68 / 151 (45.03%)	
occurrences (all)	26	100	
Vomiting			
subjects affected / exposed	11 / 152 (7.24%)	57 / 151 (37.75%)	
occurrences (all)	16	73	
Abdominal Pain			
subjects affected / exposed	9 / 152 (5.92%)	7 / 151 (4.64%)	
occurrences (all)	9	10	
Dyspepsia			
subjects affected / exposed	5 / 152 (3.29%)	12 / 151 (7.95%)	
occurrences (all)	5	13	
Abdominal Pain Upper			
subjects affected / exposed	8 / 152 (5.26%)	6 / 151 (3.97%)	
occurrences (all)	8	6	
Dysphagia			
subjects affected / exposed	1 / 152 (0.66%)	8 / 151 (5.30%)	
occurrences (all)	1	11	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	16 / 152 (10.53%)	14 / 151 (9.27%)	
occurrences (all)	18	15	
Alopecia			
subjects affected / exposed	1 / 152 (0.66%)	11 / 151 (7.28%)	
occurrences (all)	1	11	
Photosensitivity Reaction			
subjects affected / exposed	8 / 152 (5.26%)	0 / 151 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 152 (11.18%)	10 / 151 (6.62%)	
occurrences (all)	24	10	
Myalgia			
subjects affected / exposed	24 / 152 (15.79%)	3 / 151 (1.99%)	
occurrences (all)	24	3	
Back Pain			
subjects affected / exposed	12 / 152 (7.89%)	7 / 151 (4.64%)	
occurrences (all)	12	7	
Pain In Extremity			
subjects affected / exposed	6 / 152 (3.95%)	10 / 151 (6.62%)	
occurrences (all)	7	11	
Musculoskeletal Pain			
subjects affected / exposed	11 / 152 (7.24%)	3 / 151 (1.99%)	
occurrences (all)	14	3	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	13 / 152 (8.55%)	13 / 151 (8.61%)	
occurrences (all)	17	17	
Urinary Tract Infection			
subjects affected / exposed	10 / 152 (6.58%)	7 / 151 (4.64%)	
occurrences (all)	14	8	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	14 / 152 (9.21%)	14 / 151 (9.27%)	
occurrences (all)	14	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2014	Protocol version 2 The protocol was amended to comply with questions addressed during the assessment of the Voluntary Harmonisation Procedure VHP444 (VHP201415), Western Institutional Review Board request (dated June 5, 2014) to further specify protocol inclusion criterion, FDA request (dated July 10, 2014) to revise crizotinib dose modification criteria for non-hematologic toxicities to conform to the most recent FDAapproved label, as well as feedback from various other Health Authorities/Ethic Committees. Protocol BO28984 was amended to include the latest clinical and safety information.
14 May 2015	Protocol version 3 The protocol was amended to incorporate the latest pre-clinical and safety information. Changes include those to the specific timing of dose administration, pharmacokinetic objectives, concomitant therapy, and exploratory objectives.
15 April 2016	Protocol version 4 The protocol was amended to incorporate the latest safety and drug administration information. Changes include those to adverse events (AEs) relating to alectinib data and management of alectinib AEs guidelines, restrictions related to QT-prolonging concomitant medications for alectinib, and guideline for the management of missing doses of alectinib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported