Clinical trial results:
A single arm phase II trial evaluating the activity of alectinib for the treatment of pretreated RET-rearranged advanced NSCLC

Summary

EudraCT number	2017-002063-17
Trial protocol	ES BE NL SI IT
Global end of trial date	12 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	Statistical Analysis Plan (ALERT_SAP_FINAL_ANALYSIS_v1.1.pdf)

Trial information

Trial identification

Sponsor protocol code	ETOP12-17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03445000
WHO universal trial number (UTN)	-
Other trial identifiers	Roche Number: MO30176

Notes:

Sponsors

Sponsor organisation name	European Thoracic Oncology Platform
Sponsor organisation address	Effingerstr. 40, Bern, Switzerland, 3008
Public contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, regulatoryoffice@etop-eu.org
Scientific contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, regulatoryoffice@etop-eu.org

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	12 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST 1.1.

Protection of trial subjects:

Alectinib is administered until progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision. The following events are closely monitored and represent selected AEs for this trial: abnormal renal function and acute kidney injury, anaemia, bradycardia, gastrointestinal effects, hepatotoxicity, interstitial lung disease (ILD) / pneumonitis, oedema, photosensitivity, rash, severe myalgia and CPK elevations, vision disorders. All AEs, regardless of relationship to IMP, are reported from the date of signature of informed consent until 30 days after the last dose of IMP. Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with alectinib. The dose of alectinib is reduced in steps of 150 mg twice daily based on tolerability. Alectinib treatment is permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose. For women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of IMP. Men must agree to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of IMP. Women who become pregnant while participating in the trial must discontinue trial medication immediately. The pregnancy is reported following procedures detailed in the protocol. Also, any pregnancy that occurs in a female partner of a male trial participant is reported.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	14
EEA total number of subjects	14

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 15 patients have been registered in the iBioBank from 6th of November 2018 until the 1st of April 2020, with 14 of them being enrolled, coming from centers in the Netherlands, Spain, Italy and Belgium.

Pre-assignment

Screening details:

One patient was ineligible for enrolment due to active CNS metastases.

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Alectinib

Arm description:

Alectinib is administered orally, 600 mg, twice per day (1200 mg per day) until progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision.

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

Dosage and administration details:

Alectinib is administered orally, 600 mg, twice per day (1200 mg per day) until progression, refusal or unacceptable toxicity. If a planned dose of alectinib is missed, patients can take the missed dose up until 6 hours before the next dose. Patients should not take two doses at the same time to make up for a missed dose. Alectinib treatment should be permanently discontinued if the treatment interruption exceeds 21 consecutive days. The appropriate number of alectinib capsules will be provided to patients to be self-administered at home. Patients will be asked to return the remaining trial medication at each treatment visit for a compliance check. The remaining capsules will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of capsules remaining and the calculated number of capsules the patients should have taken as well as the information recorded in the patient diary must be documented and explained.

Number of subjects in period 1	Alectinib
Started	14
Completed	0
Not completed	14
Physician decision	1
Disease progression	8
Adverse event, non-fatal	3
Death	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial period
Reporting group description:	
Intention-to-treat (ITT) population	

Reporting group values	Overall trial period	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age at consent			
Units: years			
median	60.6		
full range (min-max)	38.0 to 81.4	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	4	4	
Smoking status Units: Subjects			
Current	1	1	
Former (≥ 100 cigarettes during the whole life)	3	3	
Never (0-99 cigarettes during the whole life)	10	10	
ECOG Performance Status			
0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2: Ambulatory and capable of all selfcare but unable to carry out any work activities, up and about more than 50% of waking hours.			
Units: Subjects			
ECOG PS: 0	4	4	
ECOG PS: 1	10	10	

End points

End points reporting groups

Reporting group title	Alectinib

Reporting group description:

Alectinib is administered orally, 600 mg, twice per day (1200 mg per day) until progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision.

Subject analysis set title	Efficacy cohort
Subject analysis set type	Per protocol

Subject analysis set description:

Efficacy cohort encompasses all evaluable patients, e.g. all enrolled patients excluding patients that were found to be ineligible (in retrospective review), patients that have never started the trial treatment and patients that are lost to follow-up before their first response evaluation (by RECIST 1.1). The efficacy cohort consists of 13 patients (there is one patient who was lost to follow-up before the first tumour assessment).

Subject analysis set title	Safety cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety cohort includes all patients who received at least one dose of trial treatment (i.e. all 14 patients).

Primary: Best overall response (BOR)

End point title	Best overall response (BOR)[1]

End point description:

Best overall response (OR = CR or PR), per investigator assessment. OR was determined using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). OR is defined as the best overall response [Complete Response (disappearance of all target and non-target lesions; no new lesions) or Partial Response (at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters; no new lesions)] across all assessment points. Radiological tumour assessments were performed using CT scans.

End point type	Primary

End point timeframe:

Time from enrolment of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021). The end of clinical follow-up of the last treated patient was in December 2020.

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: Trial's accrual was terminated early, with only 13 patients consisting the efficacy cohort (of the total 41 required for the statistical test of proportions).

End point values	Efficacy cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects				
Complete response	0			
Partial response	0			
Stable disease	9			
Non-Complete response/ Non-Progressive disease	1			
Progressive disease	2			
Not evaluable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control at 24-weeks

End point title	Disease control at 24-weeks

End point description:

Best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only).

End point type	Secondary

End point timeframe:

Time from enrolment of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021).

End point values	Efficacy cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Subjects				
Disease control	3			
No disease control	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival time is measured from the date of enrolment until documented progression or death, if progression is not documented. PFS is assessed according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Time from enrolment of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021).

End point values	Efficacy cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: months				
median (confidence interval 95%)	3.7 (1.8 to 7.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival time is measured from the date of enrolment until death from any cause.

End point type	Secondary

End point timeframe:

Time from enrolment of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021).

End point values	Efficacy cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13[2]			
Units: months				
median (confidence interval 95%)	99999 (13.8 to 99999)			

Notes:

[2] - 9999: Median survival time has not been reached; upper 95% confidence limit is not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability

End point title	Safety and tolerability

End point description:

The safety and tolerability of alectinib treatment is assessed through analysis of the worst grade of toxicity/adverse events according to CTCAE v4.0 criteria observed over the whole treatment period.

End point type	Secondary

End point timeframe:

Time from treatment start of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021).

End point values	Safety cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: Subjects				
Experienced adverse event(s)	14			
Experienced serious adverse event(s)	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from treatment start of the first patient until the database cut-off date for the primary BOR analysis (November 2018 - March 2021).

Adverse event reporting additional description:

Safety and tolerability of alectinib treatment is assessed through analysis of the worst grade of toxicity/adverse events according to CTCAE v4.0 criteria observed over the whole treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety cohort

Reporting group description:

The safety cohort will include all patients that have received at least one dose of trial treatment.

Serious adverse events	Safety cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death not otherwise specified (NOS)			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	6		
Fever			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
General disorders and administration site conditions - Other			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Edema limbs			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Laryngeal inflammation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders - Other			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
CPK increased			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Creatinine increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Alkaline phosphatase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cholesterol high			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
White blood cell decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dysgeusia			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Ataxia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Olfactory nerve disorder subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 6		
Blood and lymphatic system disorders - Other subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 4		
Diarrhea subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Mucositis oral subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Nausea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin and subcutaneous tissue disorders			

Dry skin subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Erythema multiforme subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Pruritus subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Skin and subcutaneous tissue disorders - Other subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Photosensitivity subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Renal and urinary disorders Urinary tract pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Bone pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Buttock pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Chest wall pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

Flank pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Mucosal infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Hyperkalemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypophosphatemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2021	Since the activation of the ALERT-lung trial, promising new agents for the treatment of RET-rearranged NSCLC have been introduced. At the same time, in a Japanese study, alectinib has shown only moderate activity in this indication. For both the aforementioned reasons, ETOP decided to prematurely close the ALERT-lung trial, by March 31, 2021. Follow-up and safety information were updated until 31 March 2021.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36030612